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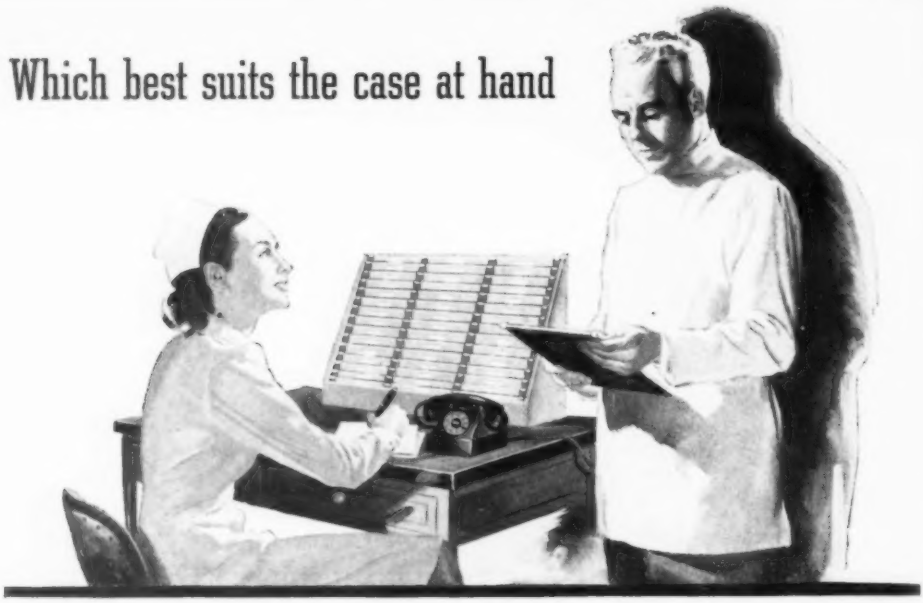
# Which best suits the case at hand



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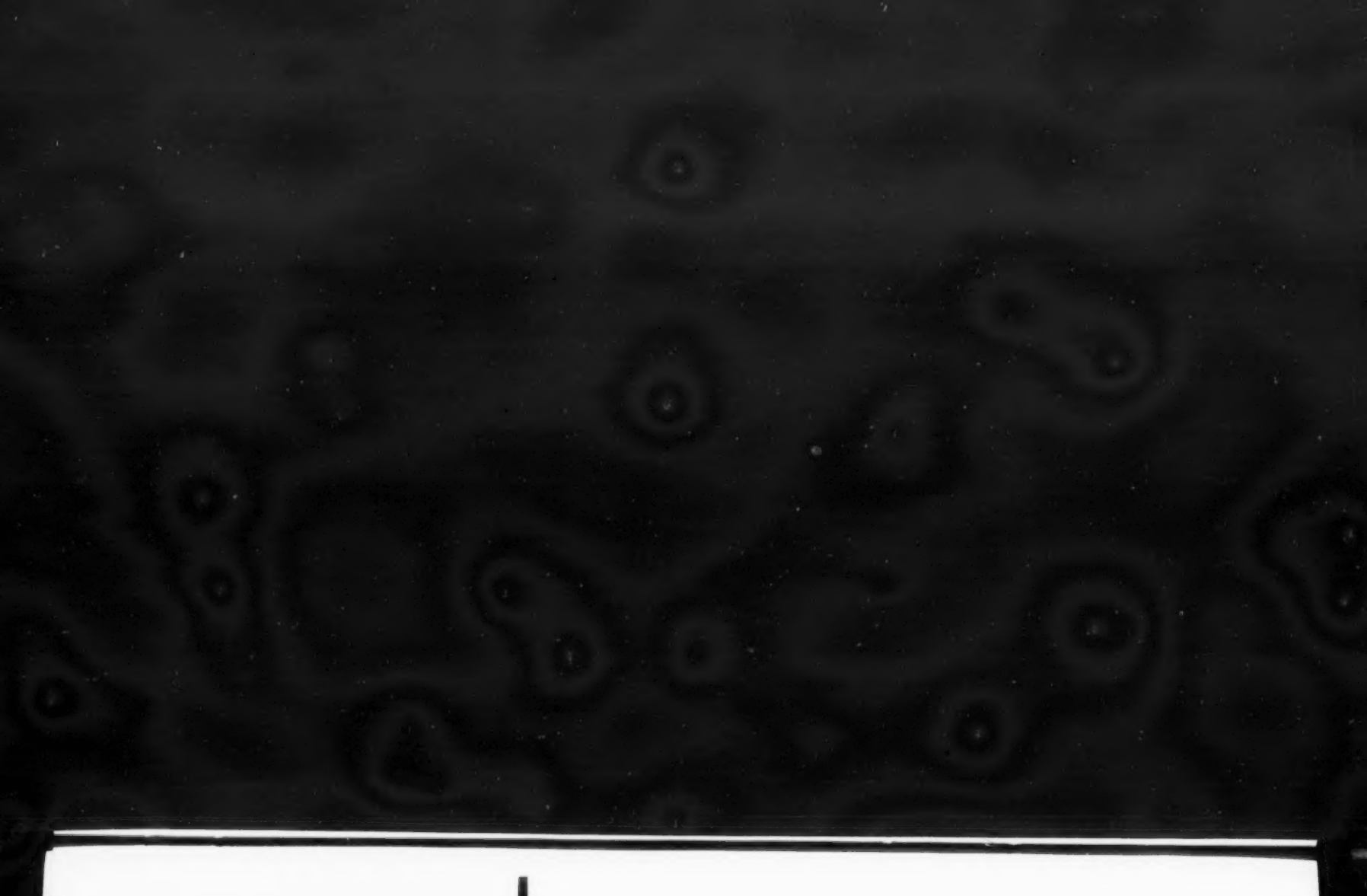

# The Journal of Pediatrics

VOL. 29 DECEMBER, 1946 NO. 6


## Original Communications

### THE DETECTION OF SUSCEPTIBILITY TO WHOOPING COUGH

#### I. INSTITUTIONAL EXPERIENCES WITH THE PERTUSSIS AGGLUTINOGEN AS SKIN TEST REAGENT


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VACCINATION against whooping cough has become a procedure of established worth,[1-3] although much remains to be learned and applied before pertussis vaccines can attain their maximal value. A simple and reliable means to aid in determining whom to vaccinate in anticipation of probable exposure becomes, therefore, a very practical need. Pertussis agglutinogen has been described and trials of this material as a skin test reagent for susceptibility to whooping cough have been reported during the past few years.[4-9] A summary of certain clinical investigations in the field are presented in this paper, together with a description of the use of agglutinogen in several institutional epidemics of pertussis.

#### REVIEW OF CLINICAL INVESTIGATION

Clinical trials of materials for skin tests in human beings were begun by using small doses of purified agglutinogen in known immune individuals.[7] This group included donors previously hyperimmunized with pertussis vaccine at the Philadelphia Serum Exchange. Reactions were obtained which resembled those found in immunized animals. The reactions appeared as early as one-half hour after injection, were often present at twenty-four hours but had usually disappeared by thirty-six or forty-eight hours. Agglutinogen has been standardized in terms of arbitrarily chosen units based on assay by adsorption of agglutinins from immune serum. One unit contains approximately 2 to 3 $\mu$g. of solids. After considerable preliminary work, the dose for clinical use was placed at 10 units of agglutinogen in 0.1 ml. normal saline. This material produced no reaction in babies between 6 and 12 months of age who had never had whooping cough or been immunized against it. In the early work, many of the reactions were checked by serum agglutination against phase I *Hemophilus pertussis* before and after the skin test. Invariably, in individuals showing an immune


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type of reaction, even if there were no circulating agglutinins detected before the test, there was a marked rise in titer following the test.

The following system of grading the reactions was established after many individuals with known histories had been tested with consistent results:

PI—*Positive-Immune:* A well indurated reaction (with or without erythema) 20 mm. or more in diameter at either one-half hour or twenty-four hours or both.

WPI—*Weakly-Positive-Immune:* An indurated reaction (with or without erythema) not exceeding 20 mm. in diameter at either one-half hour or twenty-four hours, but at least 10 mm. in diameter at either time or both.

NS—*Negative-Susceptible:* No indurated reaction at either one-half hour or twenty-four hours beyond an area 10 mm. in diameter.

It was decided to use babies in the 6- to 12-month age group as normal controls for the clinical study. The histories could be more accurately obtained in this group, and exposure would probably result in a recognized case of the disease rather than in a subclinical case of whooping cough which might give confusing results in skin testing. Further work showed that this plan was practicable.

In the early work, various substances were considered and some used for skin test controls. In some instances, a very weak dilution of horse serum was used to check a few questionable reactions. This material was chosen because horse blood had been used in the medium on which the organisms were grown. It was felt that some sensitive individual might show a nonspecific reaction to the preparation even though routine laboratory tests such as complement fixation and precipitin reactions showed no detectable amount of horse serum to be present. In about 2,000 individuals tested by these laboratories in a period of four years, only three gave much larger reactions quite different from the usual immune reaction. The intradermal injection of a very small dose of horse serum in these three children gave similar large reactions. In contrast to the material from organisms grown on horse blood, there has been no atypical reaction observed from the use of agglutinogen prepared from organisms grown on media containing human blood.

As the clinical study progressed, each group tested produced reactions which agreed with accurately known histories. It was noted, however, that many older children with negative or questionable histories gave immune or weakly immune types of reaction. In all these cases the agglutinin reaction after the test showed the presence of antibacterial antibodies. This finding seems to agree with the known augmentation in responsiveness to immunizing antigen as the result of exposure or subclinical infection. A paper by Miller and associates[10] suggests such responses to antigenic stimuli.

During the course of the clinical investigation, the value of the skin test with agglutinogen as an index of susceptibility became more evident, and, in addition, the results obtained from the serum agglutinations suggested that the material had a second and very important potentiality as a "recall" dose in all individuals with any existing immunity. The possibility of the use of agglutinogen in primary immunization has not been ignored.

EPIDEMIC IN NEW ENGLAND PEABODY HOME FOR CRIPPLED CHILDREN—INSTITUTION A

The first epidemic to be studied occurred in February, 1942, at the New England Peabody Home for Crippled Children. There were seventy-six children in the hospital at the beginning of the study. The ages ranged from 4 to 14 years and all the patients had diagnoses of chronic bone or joint disease. In reviewing the past histories it was noted that most of the patients had spent a major part of their lives in institutions. Their hospital charts represented summaries of previous institutional care with meager notes on immunization and contagious diseases. It was felt, therefore, that the past history of whooping cough or previous immunization was not entirely dependable. Two children with strong allergic histories were not included in the study.

There were nine patients with clinical whooping cough present in the hospital at the beginning of the study. These children had been isolated together in one wing of their ward. As soon as the study was started, the children with whooping cough were returned to their regular ward positions. An adequate supply of human hyperimmune pertussis serum was available if needed for the treatment of any secondary cases.

The buildings which house the patients in this institution are not modern. The wards are long and are not partitioned. The ambulatory patients mingle closely in classrooms and at meal hour, and the bed patients are put out on open porches during most of the day.

The study began in February, 1942, and was continued over a period of ten months. On the first day, measures were taken to establish a bacteriologic diagnosis of whooping cough. Hyperimmune pertussis serum was administered in the most severe cases, and the entire population of the hospital was skin tested. The treated cases responded to the serum by cessation of vomiting and decrease in the number of paroxysms.

Nasopharyngeal cultures were taken from the nine children who were isolated with whooping cough. Four of these had simultaneous exposure to cough plates with nasopharyngeal swab in place. The cultures were taken after the method described by Bradford and Slavin.[11] The swabs were planted immediately on Bordet-Gengou plates fortified with 30 per cent fresh horse blood. The cough plates were made from the same medium. The positive cultures were identified and confirmed by the use of high titer rabbit serum against phase I *H. pertussis*.

TABLE I. BACTERIOLOGIC CONFIRMATION OF WHOOPING COUGH IN INSTITUTION A

| CULTURES | ORIGINAL CASES | SECONDARY CASES |
|---|---|---|
| Total nasopharyngeal swabs | 9 | 4 |
| Number positive for phase I *H. Pertussis* | 3 | 1 |
| Total cough plates | 4 | 0 |
| Number positive for phase I *H. Pertussis* | 0 | 0 |

Table I is a summary of the results of the bacteriologic procedures which confirmed the clinical diagnosis of pertussis. Seven of the children with whooping cough were given the first dose of 20 c.c. of hyperimmune pertussis serum intramuscularly. The treatment was continued for two more doses at two-day

intervals. Two children with no evidence of existing or impending whooping cough were given serum by the same schedule in order to note the effect of the serum on the results of the skin tests and the antibody responses.

Seventy-four children were given 10 units of agglutinogen in 0.1 ml. normal saline intradermally on the first day of the study. The results were read one-half hour and twenty-four hours after the test. Forty-five of these children had a blood sample drawn before the skin test for serum agglutination. These tests were performed after the method described by Flosdorf and associates.[12] The antigen was prepared from lyophiled cultures of phase I *H. pertussis*, strain 484, which was the same strain used in the preparation of the agglutinogen. With each series of agglutinations a few samples from a preceding bleeding were used to check the reproducibility of the results. The different lots of antigen used throughout the study were tested against several sera of known potency.

No control material was used during this series of skin tests except in the case of one child who had an entirely different reaction from the usual result obtained. After a one-month interval, tests of 0.1 ml. of a 1:700 dilution of horse serum, and 0.1 ml. of a 1:10 dilution of rabbit, sheep, bovine, and human serum were given to this child. All were negative except the horse serum test, which closely resembled the original skin reaction. This child subsequently developed whooping cough.

Throughout the study, frequent blood counts were made by the resident technician on all children with suspicious coughs. The secondary cases were diagnosed entirely by shift of the blood picture and clinical findings of progressive paroxysmal cough.

The second part of the investigation was carried out approximately one month after the study was begun. Nasopharyngeal cultures were taken from four children considered to have secondary cases of whooping cough, but only one culture was positive. All of the children who had had original blood samples taken were bled again for serum agglutination.

At the end of three months there had been no additional cases of whooping cough reported in the institution. All of the children who had had original blood samples taken were bled again for serum agglutination. Skin tests were repeated on a few children from each group determined by the original skin testing. Ten months after the beginning of the study, blood samples were obtained from thirty-four of the original children who were still patients in the hospital.

*Results.*—Table I shows the bacteriologic findings in Institution A. Three positive cultures were obtained from nasopharyngeal swabs of the nine original cases of whooping cough. Simultaneous exposure of four of the children to cough plates resulted in no positive cultures. One month later, nasopharyngeal cultures were taken on four other children who had developed coughs. One of these was positive.

Table II indicates the incidence of secondary cases in relation to the reactions of the skin tests observed at the beginning of the study. The secondary

cases all occurred in children who showed susceptible or weakly immune reactions at the beginning of the study. It will be noted that immune or weakly immune reactions were observed in most of the children who had whooping cough when the study began. The disease was well established in these children so that antibacterial agglutinins had probably been produced. Because of the close correlation between the skin test reaction and the production of a detectable agglutinin titer fairly early in the disease, purified agglutinogen is not helpful in making an early diagnosis.

TABLE II. RELATIONSHIP OF INCIDENCE OF WHOOPING COUGH TO SKIN TESTING RESULTS IN INSTITUTIONAL EPIDEMICS

| INSTITUTION | INCIDENCE OF WHOOPING COUGH | SKIN TEST REACTIONS | | | TOTAL |
|---|---|---|---|---|---|
| | | NS | WPI | PI | |
| A | Original cases | 1 | 5 | 3 | |
| | Secondary cases | 6 | 2 | 0 | |
| | Total tested | 34 | 21 | 19 | 74 |
| B | No original or secondary cases (Control for Institution A) | 0 | 21 | 33 | |
| | Total tested | 0 | 21 | 33 | 54 |
| C* | Original cases | 0 | 1 | 0 | |
| | Secondary cases | 5 | 0 | 0 | |
| | Total tested | 28 | 13 | 2 | 43 |

*The chances that all the observed secondary cases could fall by random distribution into the groups indicated in Institution A and C are, respectively, less than 1 in 19 and less than 1 in 15. However, the figures on Institution C may have been altered by the fact that the susceptible children were placed in the ward by chance in proximity to the patient with whooping cough.

These figures were analyzed through the kindness of Dr. T. N. Harris of Philadelphia.

NS, Negative-Susceptible; WPI, Weakly-Positive-Immune; PI, Positive-Immune.

Table III has been compiled primarily to show the correlation between the first skin test reactions and agglutinative titer taken before and at various periods after the original skin test. All but one of the children showing a susceptible skin reaction were found to have no agglutinins for *H. pertussis* at the time of the first skin test, while those with weakly immune or immune type of reaction ranged in agglutinin titer from 0 to 1:640. Titers determined one month later showed a marked increase in most children who had had any immune skin reaction. Also, a few children with no response to the skin test later showed the presence of agglutinins. The second skin test given at three months produced an immune reaction in some of the children who previously had had only a weakly immune type of reaction. In a majority of the children with previously negative-susceptible reaction this second skin test produced a weakly immune or immune reaction. Titrations of agglutinins performed at three months after the beginning of the study showed some decrease in titer, although in a few instances there was an increase. However, the tenth-month titrations showed an increase of agglutinins in practically every child. The antigenic nature of the the skin test material, that is, its ability to elicit an agglutinin titer, is thus demonstrated.

The children who received control doses of hyperimmune serum failed to show any difference in either skin test reaction or agglutinative response.

The results of the agglutination tests one month after the first skin test (Table III, $T_2$) showed such an increase in titer that the question arose as to

TABLE III. SUMMARY OF RESULTS IN INSTITUTION A (SKIN TESTING AND TITRATION FOR AGGLUTININS)

| CASE NO. | $SR_1$ | $T_1$ | $T_2$ | $SR_2$ | $T_3$ | $T_4$ | |
|---|---|---|---|---|---|---|---|
| 1 | PI | 1:640 | 1:1,280 | PI | 1:640 | 1:5,120 | |
| 2 | PI | 0 | 0 | Δ | 320 | 40 | |
| 3 | PI | 20 | 640 | PI | 320 | 5,120 | |
| 4 | PI | 320 | 1,280 | PI | 320 | 2,560 | *Negative culture, 60 c.c. serum |
| 5 | PI | 20 | 5,120 | Δ | 640 | 2,560 | |
| 6 | PI | 0 | 0 | Δ | 80 | 1,280 | **Horse Serum positive reaction |
| 7 | PI | 0 | 320 | Δ | 80 | 160 | Positive culture, 60 c.c. serum |
| 8 | PI | 0 | 40 | Δ | 40 | 640 | |
| 9 | PI | 20 | 320 | Δ | 80 | 640 | |
| 10 | PI | 80 | 1,280 | Δ | 160 | 1,280 | |
| 11 | PI | 0 | 5,120 | Δ | 640 | 2,560 | |
| 12 | PI | 320 | 1,280 | Δ | - | 2,560 | *Negative culture, 60 c.c. serum |
| 13 | WPI | 0 | 0 | Δ | 0 | 0 | |
| 14 | WPI | 0 | 0 | Δ | 40 | 640 | ** |
| 15 | WPI | 40 | 10,240 | PI | 2,560 | 2,560 | |
| 16 | WPI | 160 | 640 | Δ | 1,280 | 2,560 | |
| 17 | WPI | 0 | 0 | Δ | 0 | 320 | |
| 18 | WPI | 80 | 160 | WPI | 80 | 2,560 | *Positive culture, 60 c.c. serum |
| 19 | WPI | 0 | 5,120 | Δ | 1,280 | 2,560 | |
| 20 | WPI | 0 | 160 | Δ | - | 2,560 | ** |
| 21 | WPI | 80 | 1,280 | Δ | - | 10,240 | |
| 22 | WPI | 80 | 640 | Δ | - | - | *Negative culture |
| 23 | WPI | 0 | 160 | PI | 20 | 1,280 | |
| 24 | WPI | 40 | 640 | Δ | 320 | 2,560 | |
| 25 | WPI | - | - | Δ | - | - | *Positive culture, 80 c.c. serum |
| 26 | WPI | - | - | Δ | - | - | * |
| 27 | WPI | - | - | Δ | - | - | * |
| 28 | NS | 0 | 0 | NS | 0 | 0 | |
| 29 | NS | 80 | 5,120 | PI | 2,560 | 5,120 | |
| 30 | NS | 0 | 40 | WPI | 20 | 160 | Given serum for control |
| 31 | NS | 0 | 0 | WPI | 160 | - | ** |
| 32 | NS | 0 | 0 | WPI | 40 | 640 | ** |
| 33 | NS | 0 | 0 | NS | 0 | 40 | |
| 34 | NS | 0 | 0 | NS | 0 | - | |
| 35 | NS | 0 | 5,120 | WPI | 1,280 | 2,560 | |
| 36 | NS | 0 | 0 | WPI | 0 | 40 | |
| 37 | NS | 0 | 160 | WPI | 40 | 2,560 | Given serum for control |
| 38 | NS | 0 | 0 | NS | 0 | 320 | |
| 39 | NS | 0 | 0 | WPI | 20 | 2,560 | |
| 40 | NS | 0 | 0 | WPI | 20 | 2,560 | ** |
| 41 | NS | - | - | Δ | - | - | * |
| 42 | NS | - | - | Δ | - | - | **Positive culture |
| 43 | NS | - | - | Δ | - | - | ** |

Samples of serum from $T_1$ were included in each series of titrations and showed original titer.

*Original cases of whooping cough.
**Secondary cases of whooping cough.
$SR_1$ First skin test reaction (at beginning of study).
$SR_2$ Result of second skin test (three months after $SR_1$).
$T_1$ Agglutinative titer original.
$T_2$ Agglutinative titer 1 month after beginning of study.
$T_3$ Agglutinative titer 3 months after beginning of study.
$T_4$ Agglutinative titer 10 months after beginning of study.
Δ Not given a second skin test.
0 In agglutinative titer column means <1:20.
NS, Negative-Susceptible; WPI, Weakly-Positive-Immune; PI, Positive-Immune.

whether this was caused by the skin test antigen, the presence of whooping cough in the institution, or by both factors. An attempt to answer this question was made by carrying out skin test and agglutination studies on children in another institution in which there was no whooping cough present.

TABLE IV. SUMMARY OF RESULTS IN INSTITUTION B (SKIN TESTING AND TITRATION FOR AGGLUTININS)

| CASE NO. | SR | $T_1$ | $T_2$ | $T_3$ | $T_4$ |
|---|---|---|---|---|---|
| 1 | PI | 0 | 1: 20 | 1: 40 | 1: 80 |
| 2 | PI | 0 | 640 | 320 | 640 |
| 3 | PI | 1:80 | 10,240 | 2,560 | 10,240 |
| 4 | PI | 0 | 1,280 | 1,280 | 1,280 |
| 5 | PI | 40 | 10,240 | 2,560 | 5,120 |
| 6 | PI | 0 | 1,280 | 640 | 640 |
| 7 | PI | 0 | 2,560 | 2,560 | 5,120 |
| 8 | PI | 160 | 2,560 | 2,560 | 5,120 |
| 9 | PI | 0 | 80 | 80 | 320 |
| 10 | PI | 0 | 5,120 | 2,560 | 2,560 |
| 11 | PI | 0 | 1,280 | 1,280 | 640 |
| 12 | PI | 0 | 5,120 | 1,280 | 1,280 |
| 13 | PI | 0 | 160 | 160 | 320 |
| 14 | PI | 0 | 1,280 | 640 | - |
| 15 | PI | 640 | 10,240 | 2,560 | - |
| 16 | PI | 0 | 10,240 | 2,560 | - |
| 17 | PI | 20 | 2,560 | 1,280 | - |
| 18 | PI | 0 | 5,120 | 2,560 | - |
| 19 | PI | 80 | 10,240 | 2,560 | - |
| 20 | PI | 0 | 5,120 | 1,280 | - |
| 21 | PI | 0 | 2,560 | 2,560 | - |
| 22 | PI | 0 | 40 | 80 | - |
| 23 | PI | 0 | 1,280 | 640 | - |
| 24 | PI | 0 | 160 | 160 | - |
| 25 | PI | 0 | 20 | 160 | - |
| 26 | WPI | 0 | 40 | 0 | 80 |
| 27 | WPI | 0 | 2,560 | 2,560 | 5,120 |
| 28 | WPI | 0 | 160 | 160 | 1,280 |
| 29 | WPI | 0 | 0 | 320 | 40 |
| 30 | WPI | - | 1,280 | 1,280 | 640 |
| 31 | WPI | 0 | 160 | 160 | 160 |
| 32 | WPI | 80 | 5,120 | 2,560 | 10,240 |
| 33 | WPI | 0 | 160 | 80 | 320 |
| 34 | WPI | 0 | 40 | 40 | 40 |
| 35 | WPI | 0 | 5,120 | 1,280 | 640 |
| 36 | WPI | 0 | 5,120 | 2,560 | 1,280 |
| 37 | WPI | 0 | 2,560 | 1,280 | 2,560 |
| 38 | WPI | ? | 10,240 | 2,560 | - |
| 39 | WPI | 0 | 320 | 320 | - |
| 40 | WPI | 0 | 160 | 160 | - |
| 41 | WPI | 0 | 0 | 0 | 0 |
| 42 | WPI | 0 | 2,560 | 1,280 | - |
| 43 | WPI | 0 | 5,120 | 2,560 | - |

SR Skin test reaction (at beginning of study).
$T_1$ Agglutinin titer before skin test.
$T_2$ Agglutinin titer one month after skin test.
$T_3$ Agglutinin titer three months after skin test.
$T_4$ Agglutinin titer ten months after skin test.
0 Agglutinin titer less than 1:20.

### CONTROL GROUP AT CHILDREN'S HEART HOSPITAL OF PHILADELPHIA—INSTITUTION B

This control study was done in the Children's Heart Hospital of Philadelphia. This is a hospital for the care of children convalescing from rheumatic fever, with approximately sixty children as patients. The group is divided into two large open wards with one floor for boys and one for girls. There are approximately thirty children in each section. The ambulatory children mingle in schoolrooms and at meals. There was no case of whooping cough in the institution at the time of the study, nor had there been any known exposure to it.

The original skin testing and serum titrations in this hospital were performed ten days later than in Institution A. Thereafter the studies were made concurrently. There were no repeated skin tests done in this institution, as all the original tests showed the immune type of reaction. The results are shown in Table II, Institution B.

Table IV shows the skin test results and agglutinin titrations at the Children's Heart Hospital of Philadelphia. The original absence or low titer of agglutinins in the presence of immune reactions to skin tests are shown also in this group of children. A marked rise in titer one month after the skin tests is also shown in this institution where there was no whooping cough present. In general, the range of titers at one month was much higher than in Institution A, and there was less decrease of titer at the end of three months. At the end of ten months the titers had been maintained or slightly increased.

The larger number of weakly immune or immune types of reactions in the children of this hospital might be due to the fact that many of them had been vaccinated against whooping cough and, in general, the entire group had spent more of their lives outside of a hospital than the children in the previous institution.

### EPIDEMIC IN ALFRED I. DU PONT INSTITUTE—INSTITUTION C

A small institutional epidemic of whooping cough was observed in the Alfred I. du Pont Institute of the Nemours Foundation, in the spring of 1943. There was one case of clinical whooping cough at the onset of the study. This child had been removed from the open ward into very complete isolation.

This institution has been built and planned so that the children are separated into small groups, and there is less intermingling than in either of the two institutions previously discussed. In the wards, although there are no partitions, there is ample space between the beds. The plan of study in this institution was similar to that already reported. A nasopharyngeal swab was taken from the child who had whooping cough in an attempt to establish the organism, with a negative result.

All the children were given 10 units of agglutinogen in 0.1 ml. of normal saline intradermally after the case of whooping cough was diagnosed. Results of the skin testing are shown in Table II, Institution C. Eight of the smaller children with the susceptible type of reaction were given hyperimmune pertussis serum for prophylaxis in about one-half the recommended dosage (20 ml. instead of 40 ml.).[13] Five secondary cases of whooping cough developed in this group. All of these cases developed in children who were situated near the bed of the child who had the original case. The secondary cases were all very mild and again were only diagnosed by the shifting blood counts on the children who developed coughs. Only one child of this group had a cough severe enough to cause vomiting. Agglutinin titrations were omitted in this study.

### DISCUSSION

When clinical investigation was first begun, the individuals to be tested were chosen on the basis of history of the disease. As the work progressed,

it became evident that there were many persons without known history of whooping cough in whom immunity was demonstrated by the skin test reaction, and this immunity further indicated by serum agglutination. This immunity could have developed as the result of exposure or subclinical infection.

The apparent widespread occurrence of partial immunity as indicated by the skin test renders questionable the value of classification of results on the basis of past history. The young infants with no history of whooping cough give skin test results compatible with their history. They invariably give a negative-susceptible reaction even to large doses of agglutinogen. Large numbers of serum agglutinations before and after skin testing have shown that a demonstrable titer has followed in all but a very few patients who had an initial immune skin test reaction. This rise in titer has been found at approximately the end of the first week after the skin test in any immune individual, even though agglutinins were absent before the skin test. This appears to be one of the most significant findings in these studies. The protection afforded the susceptible and weakly-positive-immune children by the skin test in Institution A is believed to have contributed to reducing the number of secondary cases. The presence of pertussis in Institution A as well as the antigenicity of the first skin test could together produce the reversal of the skin test in many individuals who were retested. Further data (to be published) show that a single skin test dose of agglutinogen may produce a slight rise in agglutinin titer as well as a feeble reaction to a second skin test. A third skin test will often show a definitely positive-immune reaction with an agglutinin titer as high as 1:640 or 1:1,280.

## SUMMARY

A purified agglutinogen of phase I *H. pertussis* was used as a skin test reagent in three institutions.

An epidemic of whooping cough was studied in detail; all secondary cases occurred in children whose skin tests indicated susceptibility or weak immunity.

Routine agglutination tests indicated the value of agglutinogen as a "recall" dose, as shown by the small number of cases following skin testing of the entire population of the institution.

Parallel studies were done in an institution in which there was no whooping cough, in order to rule out the effect of the presence of the disease on the skin test reaction and agglutinative titer of exposed individuals. The effectiveness of the skin test reagent as an antigen was well established by the results obtained in this control institution.

In a second institution in which one case of whooping cough appeared, all secondary cases occurred in individuals who had had negative skin tests.

We wish to express our appreciation to Dr. Gerald Hoeffel, Medical Director of the New England Peabody Home, who assisted in planning the studies in that institution, and to Dr. Ella Roberts, Medical Director of the Children's Heart Hospital of Philadelphia, by whose permission the studies there were made possible. We appreciate the assistance of Dr. Amedeo Bondi, Department of Bacteriology, Temple University School of Medicine, in making the bacteriologic studies.

## REFERENCES

1. Felton, H. M, and Willard, C. Y.: J. A. M. A. **126**: 294, 1944.
2. Cravitz, L., and Cauley, J. H.: J. A. M. A. **129**: 539, 1945.
3. Cohen, S. M., and Wheeler, M. W.: Am. J. Pub Health **36**: 371, 1946.
4. Flosdorf, E. W., Kimball, A. C., and Chambers, L. A.: Proc. Soc. Exper. Biol. & Med. **41**: 122, 1939.
5. Flosdorf, E. W., and Kimball, A. C.: J. Immunol. **39**: 287, 1940.
6. Flosdorf, E. W., and Kimball, A.: J. Immunol. **39**: 475, 1940.
7. Flosdorf, E. W., and McGuinness, A. C.: Am. J. Dis. Child. **64**: 43, 1942.
8. Felton, H. M., and Flosdorf, E. W.: J. PEDIAT. **22**: 259, 1943.
9. Flosdorf, E. W., Felton, H. M., Bondi, A., and McGuinness, A. C.: Am. J. M. Sc. **206**: 421, 1943.
10. Miller, J. J., Silverberg, R. J., Saito, T. M., and Humber, J. B.: J. PEDIAT. **22**: 637, 1943.
11. Bradford, W. L., and Slavin, B.: Proc. Soc. Exper. Biol. & Med. **43**: 590, 1940.
12. Flosdorf, E. W., McGuinness, A. C., Kimball, A. C., and Armstrong, J. G.: J. PEDIAT. **19**: 638, 1941.
13. McGuinness, A. C., Armstrong, J. G., and Felton, H. M.: J. PEDIAT. **24**: 249, 1944.

# THE DETECTION OF SUSCEPTIBILITY TO WHOOPING COUGH

## II. Clinical Standardization of the Diagnostic Skin Test Reagent and Its Use in Institutional and in Private Practice

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CLINICAL studies of the agglutinogen skin test for susceptibility to whooping cough which have been reported previously have concerned the original sonic-extracted agglutinogen as described by Flosdorf.[1] A simplified method of preparing agglutinogen by chemical extraction has been described subsequently by Smolens and Mudd.[2]

Preliminary laboratory trials with this acid-extracted agglutinogen (referred to as E-1) indicated that it was similar to sonic-extracted agglutinogen (A-1) with respect to absence of toxicity, positive skin reactions in immune animals, and ability to stimulate agglutinins against *Hemophilus pertussis*. In addition, the yield of purified agglutinogen by this chemical process was greater than by the sonic method. This newly prepared agglutinogen was assayed by agglutinin adsorption of high titer phase I pertussis serum, and the unit dosage was recommended from this procedure. This method of standardization has been used by Flosdorf.[1]

### CLINICAL STANDARDIZATION OF AGGLUTINOGEN AS SKIN TEST REAGENT

A preliminary clinical trial was made to compare this newly prepared agglutinogen with sonic-extracted agglutinogen. Known immune individuals with high agglutinin titers against phase I *H. pertussis* were chosen from the donors at the Philadelphia Serum Exchange. Babies from 6 to 12 months of age with no recorded history of whooping cough were chosen for the susceptible group. Twenty-five immune donors were injected intradermally in the right arm with 10 units of sonic-extracted agglutinogen in 0.1 ml. isotonic saline, and 10 units of acid-extracted agglutinogen in 0.1 ml. isotonic saline was given in a similar position on the left arm. All of the reactions were observed daily for one week. The findings were uniform in each group. The immune donors showed an immediate reaction in one-half hour consisting of a wheal with a flare of erythema. The size of this reaction was slightly larger on the left (E-1) arm than the right (A-1). At twenty-four hours these individuals all had large reactions on both arms. There was induration and erythema, with no tenderness, on each arm. In some instances the areas measured 50 to 60 mm. in diameter. Again the total size was somewhat larger on the left (E-1) arm, the induration much more evident, and the erythema more marked. The reaction on the right (A-1) arm began to disappear after twenty-four to thirty-six hours, and there was no residual pigmentation observed in any instance. At the same time, reactions to the acid-extracted agglutinogen began to fade but were evident for several days longer. In some instances faint pigmentation remained.

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Sixteen babies were tested on the same day in a similar manner with 10 units of each material. There was no reaction observed on either arm of any baby during the seven-day observation period. A few babies were then given as much as 50 units of acid-extracted agglutinogen with no skin reaction evident at any time during a similar seven-day observation period. The results of this first trial are shown in Table I.

TABLE I. SPECIFICITY OF ACID- AND SONIC-EXTRACTED AGGLUTINOGEN* IN KNOWN IMMUNE AND SUSCEPTIBLE INDIVIDUALS

| | SKIN TEST REACTIONS | | | | | | |
|---|---|---|---|---|---|---|---|
| | NEGATIVE-SUSCEPTIBLE | | WEAKLY-POSITIVE-IMMUNE | | POSITIVE-IMMUNE | | TOTAL |
| | $A_1$ | $E_1$ | $A_1$ | $E_1$ | $A_1$ | $E_1$ | |
| Infants (Susceptible) | 16 | 16 | 0 | 0 | 0 | 0 | 16 |
| Adults (Immune) | 0 | 0 | 0 | 0 | 25 | 25 | 25 |

*Ten units of each material per 0.1 ml.
$A_1$ Sonic-extracted agglutinogen.
$E_1$ Acid-extracted agglutinogen.

Further experiments to establish a satisfactory dose of acid-extracted agglutinogen were made by performing parallel tests with sonic-extracted agglutinogen on fifty-nine children in the Children's Heart Hospital of Philadelphia. The status of immunity in many of these children had been established by a previous skin test with 10 units of sonic-extracted agglutinogen.[3] In this group, a comparison was made by means of 5 units of each material in 0.1 ml. of isotonic saline. It was found in several cases that this amount of sonic-extracted agglutinogen was not sufficient to produce an immune type of reaction in an individual who had previously given an immune type of reaction to 10 units of the same material. In general, the reaction to acid-extracted agglutinogen was almost twice as large in diameter as the reaction to sonic-extracted material. In many cases when both reactions were of a weakly immune type at the end of one-half hour, the reaction to the sonic material had disappeared in twenty-four hours, while that to the acid fraction was of the strongly immune type. After this series of tests it was decided to discontinue any readings earlier than twenty-four hours. Review of the skin test results up to that time indicated that all twenty-four-hour positive reactions had been positive in one-half hour also. The results of this study shown in Table II indicated that 5 units of acid-extracted agglutinogen gave satisfactory results in a group with known immunity. The intensity of the reactions after 5 units of acid-extracted agglutinogen suggested that the dosage might be decreased still more.

TABLE II. SENSITIVITY OF ACID- AND SONIC-EXTRACTED AGGLUTINOGEN* (IN IMMUNE INDIVIDUALS)

| | SKIN TEST REACTIONS | | | |
|---|---|---|---|---|
| | NEGATIVE-SUSCEPTIBLE | WEAKLY-POSITIVE-IMMUNE | POSITIVE-IMMUNE | TOTAL |
| $A_1$, Sonic-extracted agglutinogen | 28 | 29 | 2 | 59 |
| $E_1$, Acid-extracted agglutinogen | 5 | 19 | 35 | 59 |

*Five units/0.1 ml.

A group of children from the surgical and orthopedic wards at the Children's Hospital with previous histories of whooping cough were chosen for this further testing. Four groups of five or more children were used. Each group was given one of the following doses: 2.5, 1, 0.5, and 0.25 units in 0.1 ml. of isotonic saline. The results are shown in Table III.

TABLE III. THE ANTIGENIC EFFECT OF SERIAL DOSES OF ACID-EXTRACTED AGGLUTINOGEN ON AGGLUTINATIVE TITER

| CASE NO. | UNITS OF AGGLUTINOGEN | SKIN TEST REACTION | AGGLUTININ TITER BEFORE SKIN TEST | AGGLUTININ TITER ONE WEEK AFTER SKIN TEST |
|---|---|---|---|---|
| 1 | | PI | 1:20 | 1:1,280 |
| 2 | | PI | <1:20 | 1:1,280 |
| 3 | | PI | 1:20 | 1:160 |
| 4 | 2.5 | WPI | <1:20 | 1:640 |
| 5 | | WPI | <1:20 | 1:2,560 |
| 6 | | NS | <1:20 | <1:20 |
| 1 | | PI | <1:20 | 1:160 |
| 2 | | PI | <1:20 | 1:2,560 |
| 3 | 1.0 | PI | <1:20 | 1:320 |
| 4 | | PI | 1:80 | 1:2,560 |
| 5 | | NS | <1:20 | <1:20 |
| 6 | | NS | <1:20 | <1:20 |
| 7 | | NS | <1:20 | <1:20 |
| 8 | | NS | <1:20 | 1:40 |
| 1 | | WPI | 1:80 | 1:640 |
| 2 | | WPI | <1:20 | 1:320 |
| 3 | 0.5 | WPI | 1:40 | 1:320 |
| 4 | | WPI | <1:20 | 1:80 |
| 5 | | NS | <1:20 | <1:20 |
| 1 | 0.25 | WPI | <1:20 | 1:640 |
| 2 | | WPI | <1:20 | 1:80 |
| 3 | | WPI | <1:20 | 1:160 |
| 4 | | WPI | 1:20 | 1:80 |
| 5 | | NS | <1:20 | <1:20 |

NS Negative-Susceptible.
WPI Weakly-Positive-Immune.
PI Positive-Immune.

These results reveal that an immune child can give a positive reaction to very small doses of E-1. From the data in this series of skin tests it was felt that one unit of E-1 could be used satisfactorily for further work. The antigenic effect of these small doses is not as great as that of larger doses. This series of cases is very small, and again shows that immunity cannot always be predicted by history alone.

### MANAGEMENT OF AN INSTITUTIONAL EPIDEMIC

During the time that fractional doses of acid-extracted agglutinogen were being tried, another trial with simultaneous doses of acid-extracted and sonic-extracted agglutinogen was made at the Pennsylvania School for the Deaf. This institution had had an unusually severe outbreak of whooping cough in 1942, with about forty cases, and the records prior to 1942 showed that an outbreak of whooping cough had occurred almost yearly.

The children live in unusually close contact in both schoolrooms and dormitories because of their disability. There had never been a routine immunization

program against pertussis. The school records were very accurate, and the past histories were felt to be unusually reliable because parents are likely to remember illnesses in defective children quite well. These children do not lead an entirely closed institutional life but often spend week ends and long vacations with their families. It is, therefore, easy to understand the frequent incidence of pertussis in this school.

The investigation was started in this group in May, 1943, with the hope that the next outbreak of whooping cough could be better studied and controlled. One hundred sixty-one children were tested simultaneously with 10 units of sonic-extracted material and 5 units of acid-extracted material. The reactions were more nearly parallel in size than the reactions at the Heart Hospital, where 5 units of each material were used, but the intensity of the E-1 reaction was again greater. In the group which had simultaneous skin tests, twenty-three of the children predicted to be susceptible gave delayed positive reactions which appeared on about the sixth day and lasted about twenty-four hours. These reactions were similar to the immune type of reaction in other children. In all cases the secondary reaction to E-1 was as strong or stronger than to A-1 (sonic-extracted agglutinogen). Forty-two immune children showed a similar delayed reaction on the sixth day. In checking the histories, it was found that many of these children had been exposed to previous epidemics in this institution but had not contracted whooping cough. The others had past histories of whooping cough. In November, 1943, the forty-six new students of the fall semester were tested with one unit of E-1, since this dosage had been demonstrated to give a satisfactory response. No delayed reactions were observed in this group. The classification of the children by the skin test results is shown in Table IV.

TABLE IV. SKIN TEST RESULTS IN PENNSYLVANIA SCHOOL FOR DEAF

| GROUP | AGGLUTINOGEN UNITS | | SKIN TEST REACTIONS | | | |
|---|---|---|---|---|---|---|
| | | | NS | WPI | PI | TOTAL |
| April, 1943, residents | $A_1$ | 10 | 47 | 67 | 47 | 161 |
| | $E_1$ | 5 | 47 | 67 | 47 | 161 |
| November, 1943, new students | $E_1$ | 1 | 31 | 9 | 6 | 46 |
| April, 1944, children previously NS | $E_1$ | 1 | 5 | 15 | 46 | 66 |

NS Negative-Susceptible.
WPI Weakly-Positive-Immune.
PI Positive-Immune.

At the beginning of December, 1943, three weeks after the new students were tested, the first case of whooping cough developed in the primary section of this institution. Skin test results were available on 207 children before the outbreak of whooping cough. Because of the possibility of starting a large epidemic, the child who first developed whooping cough was immediately withdrawn from the classroom and dormitory. In spite of the isolation of this child, four more cases developed within the next two weeks. All of these cases were among the children who were classified as susceptible by the skin test. Bacteriologic study of this epidemic resulted in four nasopharyngeal cultures showing typical phase I *H. pertussis*.

The approach of the Christmas holiday produced a crisis in the management of the institution. By special permission from the local boards of health, arrangements were made to send home all the children susceptible according to the agglutinogen skin test. By this procedure it was hoped to shorten the epidemic. The four children with secondary cases of whooping cough were allowed to continue in their normal dormitory and class routine. During the Christmas holiday, five other children developed clinical whooping cough at home. No cultures were taken. Table V summarizes the incidence of whooping cough in this group of children who had been previously skin tested. No case developed among the children remaining at school in spite of the fact that four children with proved whooping cough were put back into the school routine.

TABLE V. INCIDENCE OF WHOOPING COUGH IN RELATION TO CLASSIFICATION BY SKIN TESTING IN PENNSYLVANIA SCHOOL FOR THE DEAF

| CASES OF WHOOPING COUGH ACCORDING TO SKIN TEST REACTIONS | | | |
|---|---|---|---|
| NEGATIVE-SUSCEPTIBLE | WEAKLY-POSITIVE-IMMUNE | POSITIVE-IMMUNE | TOTAL |
| 10 | 0 | 0 | 10 |

In April, 1944, skin tests were performed on sixty-six of the previously susceptible children. The results showed five of them still of the susceptible type, fifteen of the weakly immune type, and forty-six to be now definitely immune. These results are shown in Table IV.

It was not possible to do routine agglutinations on this entire group. One week after the repeat skin testing in April, representative cases were chosen for serum agglutination. Three children with susceptible skin reactions were bled. In two, the agglutinative titer was negative, and in the third, the titer was 1:320. Seven children who had whooping cough in December, 1943, were bled. All of them showed immune or weakly immune skin reactions, and titers ranged from 1:20 to 1:2,560. Three children with the weakly immune type of reactions were bled and the titers ranged from 1:80 to 1:1,280. Four other children showing the immune type of skin reaction in the original testing were bled and in all instances the titer was 1:1,280 or 1:2,560.

Observation of this school group has been continued. As each semester begins, the new students are skin tested with acid-extracted agglutinogen. The susceptible ones are given routine immunization with a standard phase I vaccine. There has been no case of whooping cough in the institution since the outbreak reported in this paper.

### COMPARATIVE SKIN TESTS WITH AGGLUTINOGEN AND WITH TOXIN

The final episode of the clinical investigation of agglutinogen was the comparison of this fraction of phase I *H. pertussis*, which demonstrates the presence of antibacterial immunity, with another material for skin testing developed by Strean.[4] This material, described as a toxin, has been used for the purpose of determining the presence of antitoxic immunity. It gives a positive or primary irritative reaction in the skins of individuals with no antitoxic antibodies. Individuals with antitoxic antibodies should have no reaction to this material if it

be a pure toxin. The interpretation of these reactions is exactly opposite to the agglutinogen skin test results. A summary of the expected reactions from each skin test material follows:

| | SUSCEPTIBLE | IMMUNE |
|---|---|---|
| Agglutinogen Test | negative | positive |
| Toxin Test | positive | negative |

Early in 1945 there was an opportunity to observe the results of simultaneous skin tests using the toxin and phase I agglutinogen. Children were chosen from two health centers under the direction of the Division of Maternal and Child Hygiene of the Department of Public Health of Philadelphia. The test groups were set up from Department of Public Health records under headings of (1) immunized, (2) history of whooping cough, and (3) history of no immunization or whooping cough. The tests were placed on opposite arms at the same time, one physician administering the toxin test, another, the agglutinogen test. The doses were one skin test unit of toxin as defined by Strean and one unit of acid-extracted agglutinogen. All readings were made at the end of twenty-four hours.

TABLE VI. COMPARISON OF TOXIN AND AGGLUTINOGEN SKIN TESTS

| HISTORY FOR PERTUSSIS | TEST REAGENT | RESULTS | | | TOTAL |
|---|---|---|---|---|---|
| | | IMMUNE | SUSCEPTIBLE | DOUBTFUL | |
| *Health Center A* | | | | | |
| Vaccinated | Agglutinogen | 42 | 21 | 2 | 65 |
| | Toxin | 1 | 64 | | 65 |
| History of whooping cough | Agglutinogen | 3 | 9 | | 12 |
| | Toxin | 2 | 10 | | 12 |
| No history of whooping cough or vaccination | Agglutinogen | 2 | 26 | | 28 |
| | Toxin | 0 | 28 | | 28 |
| | | | | | 105 |
| *Health Center B* | | | | | |
| Vaccinated | Agglutinogen | 117 | 31 | | 148 |
| | Toxin | 3 | 42 | | 45 |
| History of whooping cough | Agglutinogen | 1 | 0 | | 1 |
| No history of whooping cough or vaccination | Agglutinogen | 3 | 44 | | 47 |
| | Toxin | 2 | 10 | | 12 |
| | | | | | 196 |

At one center, 105 children were tested with both materials; at the other, 197 children were tested with agglutinogen and only fifty-seven with toxin. The results shown in Table VI indicate clearly that the toxin test is of little value in any group which has been immunized with standard phase I whole pertussis vaccine. The children who gave positive-immune reactions after agglutinogen also gave positive reactions with toxin test material on the opposite arm. The readings on the toxin test suggest that the expected result was confused by the presence of agglutinogen in the toxin test material.

A recent paper by Cravitz and Williams[5] reported similar findings in a series of immunized children from Boston health centers tested for susceptibility by the toxin. These workers used heated toxin for a control test in their

study. They concluded that the large percentage of positive reactions in these immunized children must be considered to be due to the presence of agglutinogen, since the toxin had been destroyed by heat.

At both centers the children with no history of whooping cough or immunization gave the large pink reaction after the toxin test. These children showed no reaction at the site of the agglutinogen test. This group gave the only clear-cut reactions to the toxin test.

Analysis of the records showed that a large number of the vaccinated children with susceptible reactions had been vaccinated several years before when the vaccine used in the City Health Centers had been prepared from strains of questionable antigenicity, and the interval between the doses was shorter than that used at present. Further tests with agglutinogen in groups vaccinated with later vaccines gave a much higher number of immune reactions.

## DISCUSSION

The value of purified agglutinogen in the determination of susceptibility to whooping cough has been demonstrated by reports of its use in large numbers of children.[6-8] The logical sequel to reports of a new biological is the appearance of more simplified and practical methods of preparing a product which will meet the specifications of the original material.

The clinical observations reported here show the evolution of a satisfactory material, dosage schedule, and reading time. The dosage set for the original sonic-extracted agglutinogen was determined first in the laboratory, and then finally by trial in human beings. The predicted dose seemed to be satisfactory. Acid-extracted agglutinogen was studied by the same method but had to be finally standardized in human beings because the predicted dose was stronger than the dose of sonic-extracted agglutinogen determined by the same technique. At the present time the composition of agglutinogen is not known. Until there has been further biochemical study of this product, standardization in human beings is probably the only satisfactory method of assay. The selection of a suitable control for this method of assay must be carefully planned. At present, new lots of agglutinogen are assayed by laboratory methods and then tested in known immune individuals in order to determine the smallest dose that will give a well-defined, positive reaction. The immune status of the test individual is established by a parallel skin test with agglutinogen, the potency of which has been established after long clinical study. The specificity of the reaction and the absence of toxin in any new agglutinogen must be established by giving relatively large doses intradermally to susceptible infants.

The optimal time for reading the test has been placed at twenty-four hours. At first the readings were made at one-half hour, four hours, and twenty-four hours. Careful determinations of agglutinins indicated that all individuals with a positive or immune reaction which persisted for twenty-four hours showed a subsequent rise in agglutinin titer. Although many individuals showing a positive reaction at the end of one-half hour and not showing it at twenty-four hours show a rise in agglutinin titer, the danger of mistaking a nonspecific, immediate reaction in the skin for an immune reaction must be considered. The

recommended twenty-four-hour reading has been entirely satisfactory in more recent studies with agglutinogen.

As a result of the experience to date, a simple classification of individuals as immune or susceptible has been adopted. An area of induration and erythema of 1 square centimeter or more, which may be present at one-half hour but must be present at twenty-four hours after the intradermal administration of one skin test dose of pertussis agglutinogen, is considered an immune reaction. A reaction less than this or no reaction is considered to indicate susceptibility.

The delayed reactions which have been observed on the sixth day following doses of 5 or 10 units of agglutinogen come exactly at the time when the agglutinin titer begins to rise. Correlation of past histories with the incidence of delayed reactions indicates that individuals with "contact immunity" may show this reaction. Ratner's theory[9] of local serum sickness may explain this phenomenon.

Comparison of the agglutinogen test with the Strean toxin test gave clear demonstration of the unsatisfactory results obtained with this toxin in attempting to evaluate the immune status of any group which had been vaccinated with standard phase I whole pertussis vaccine. The toxin test gave the expected reaction only in the susceptible children. Two reasons may be suggested to explain the unsatisfactory reactions seen in the vaccinated children. If traces of agglutinogen were present in the toxin, the positive reactions seen in the children predicted by agglutinogen to be immune would be explained. In the susceptible children, the presence of agglutinogen in the testing material would not interfere with the primary toxic reaction which indicates susceptibility by the toxin test. The work of Cravitz and Williams[5] shows that after immunization even with a vaccine combined with toxoid, very little or no circulating antitoxin can be detected after six months. Therefore, the toxin test cannot be expected to measure immunity in any population immunized with standard vaccines.

Agglutinogen has been used in private practice as part of the routine for preschool examination. It is of double value in demonstrating the existence of immunity to pertussis several years after primary immunization, and in stimulating that immunity. If the child seems to be susceptible, another course of immunization is given. In this way it may be possible to prevent the occurrence of pertussis in the older children by maintaining more adequately the immunity after primary vaccination.

## SUMMARY

The agglutinogen of phase I *H. pertussis* prepared by a method of chemical extraction has been compared with the sonic-extracted material which has been shown to be a satisfactory skin test agent for susceptibility to pertussis.

The acid-extracted agglutinogen was standardized against the sonic product and found to be more potent, and to give more clear-cut reactions.

Review of these data showed that a twenty-four-hour reading time could be recommended.

At present the skin test dose is estimated in units by laboratory methods, and assayed finally by human intradermal inoculation.

This agglutinogen gives identical results to those obtained with the sonic-extracted material; there is no reaction even in large doses in normal (susceptible) individuals, and an allergic reaction at the site of injection in any individual with solid immunity to whooping cough from either immunization or previous attack of the disease.

In an institution with annual outbreaks of whooping cough, the use of agglutinogen before the anticipated epidemic was followed by a significant decrease in the number of cases, all of which occurred in the group predicted by the skin test to be susceptible. Yearly skin testing of new students followed by immunization of all susceptible children has resulted thus far in the absence of whooping cough from this school.

Comparison of the agglutinogen skin test with the Strean toxin test in children from City of Philadelphia Health Centers has been made. The results clearly indicated a close correlation between the history and the agglutinogen skin test results. On the other hand, results from the use of the Strean test revealed that satisfactory correlation between history and toxin test only existed in the group of known susceptible children.

The use of agglutinogen has a definite place as a public health measure in periodic examinations of young children. The duration of primary immunization may be determined while the antigenicity of agglutinogen produces a prompt recall of any existing antibacterial immunity.

We acknowledge with gratitude the cooperation and continued interest of the medical board and teaching staff of the Pennsylvania School for the Deaf. The work in the city health centers of Philadelphia was carried out by the permission of Dr. Harriet L. Hartley and Dr. Dorothy Wood. Miss Elsie Robbins, principal bacteriologist of the Department of Laboratories of the City of Philadelphia, assisted in analyzing these data obtained in the city health studies.

## REFERENCES

1. Flosdorf, E W., and Kimball, Anne C.: J. Immunol. **39**: 475, 1940.
2. Smolens, Joseph, and Mudd, Stuart: J. Immunol. **47**: 155, 1943.
3. Felton, Harriet M., and Flosdorf, Earl W.: J. PEDIAT. **29**: 677, 1946.
4. Strean, L. P.: Canad. M. A. J. **42**: 525, 1940.
5. Cravitz, L., and Williams, J. W.: J. PEDIAT. **28**: 172, 1946.
6. Flosdorf, E. W., Felton, H. M., Bondi, A., and McGuinness, A. C.: Am. J. M. Sc. **206**: 421, 1943.
7. Felton, Harriet M., and Flosdorf, Earl W.: J. PEDIAT. **22**: 259, 1943.
8. Sauer, L. W., and Markley, R. N.: J. A. M. A. **131**: 967, 1946.
9. Ratner, Bret: Allergy, Anaphylaxis and Immunotherapy, Baltimore, 1943, Williams & Wilkins, p. 423.

# HYPOFUNCTION OF THE ADRENALS IN EARLY LIFE

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IN THE newborn period and early weeks of life there are observed not infrequently certain symptoms resulting from hormonal imbalance and some apparent difficulty in adjustment of the endocrine mechanism by the infant. Familiar examples are: (1) Physiologic lactation, menstruation, and involution of the uterus of the newborn due to the placental transmission of estrogen and prolactin to the infant's circulation from the mother; (2) hypoglycemia and hyperinsulinism of the newborn which we have discussed in detail previously;[1] and (3) a low calcium tetany apparently due to a physiologic hypoparathyroidism resulting from a maternal hyperparathyroidism that is physiologic during pregnancy.

Most of these disturbances are transient, although occasionally the symptoms may persist for several weeks. Analogous symptoms referable to abnormal hormonal activity of the adrenal glands, except for the serious acute symptoms of adrenal hemorrhage (Waterhouse-Friderichsen syndrome) and rare cases of macrogenitosomia and pseudohermaphroditism associated with symptoms and signs of Addison's disease,[2-4] have not been recognized as a clinical entity. It is the purpose of this paper to present certain clinical observations which give support to the view that hypofunction of the adrenal cortex at times may produce disturbances in the metabolism of young infants.

Interest in the possibility of recognizing symptoms of adrenal cortical insufficiency in certain infants was stimulated by the author's recent observation of an infant with Addison's disease in whom a pronounced tendency to dehydration, asthenia, weight loss, hypoglycemia, anorexia, intermittent vomiting, and loose stools were the prominent symptoms.[5] Such symptoms in young infants are not infrequent and may result from a number of causes.

There is a small group of apparently physically normal premature and full-term infants frequently referred to as "constitutionally inferior" because of inability to thrive despite adequate medical and nursing care. This type of infant is usually weak, takes food reluctantly, and may manifest some or all of the symptoms exhibited by patients with Addison's disease. The pathologist is usually of no assistance in determining the cause of these "metabolic" deaths. This is the type of patient which we thought might be benefited by the administration of adrenal hormones.

Much progress has been made in understanding the physiologic function of the adrenal cortex from work on experimental animals and the study of Addison's disease. Loeb[6] showed that the sodium levels may be low and the potassium levels high in Addison's disease. It is generally known that there is a decreased ability of the renal tubules to reabsorb sodium, and, as a result, there is a decreased concentration of sodium in the blood, a corresponding fall in blood bi-

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carbonate, chloride, or both, increase in plasma protein, decrease in plasma volume, decrease in rate of blood flow, increase in excretion of chloride, steady loss of weight, dehydration, refusal of food, vomiting, increase in nonprotein nitrogen, muscular weakness, and anuria when shock is extreme.

Normal intestinal function may be to a great extent dependent upon the activity of the true cortex. After removal of the adrenals in experimental animals, anorexia may be pronounced. In addition, there may be a tendency to intermittent intestinal upsets with vomiting, diarrhea, or both. These complaints are part of the picture in Addison's disease.[7] Many animal experiments[8-13] have demonstrated that adrenalectomy markedly impairs the intestinal absorption of water, glucose, sodium chloride, and potassium, and alters the ability of the body membranes to maintain proper gradients of concentration of certain salts. Tuerkischer and Wertheimer,[14] in their experiments on adrenalectomized rats, and Thaddea,[15] in his study of the gastric secretions in patients with Addison's disease, indicated that the secretion of rennin, pepsin, and hydrochloric acid is dependent upon normal adrenal function.

The adrenal cortex has a significant part to play in carbohydrate metabolism. Cori and Cori[16] and Britton and Silvette[17] effectively demonstrated depletion of liver glycogen and consequent hypoglycemia in adrenalectomized animals. Most physiologists feel that the adrenal cortical hormones cause decreased utilization of glucose with a consequent rise in blood sugar; however, this theory has not been definitely proved. It is agreed that the hormones increase glycogen storage in the liver[18] and abolish hypoglycemia in adrenalectomized animals and in Addison's disease, and increase glyconeogenesis from body proteins. Desoxycorticosterone acetate has no direct effect on carbohydrate metabolism.

Because of these many physiologic functions that are directly or indirectly the responsibility of healthy adrenals, it is well to consider the possibility of hypofunction of the adrenals when dealing with unexplained, protracted illnesses of premature and young infants, especially those illnesses associated with anorexia, vomiting, loose stools, persistent tendency to dehydration, hypoglycemia, and failure to gain weight, after adequate nursing and medical procedures have failed to restore the infant to normalcy.

The following cases present a variety of symptoms ranging from attacks of hypoglycemia, anorexia, listlessness, and failure to gain weight, to unexplained, protracted diarrhea. The "present illness" in every patient began in the neonatal period. A brief summary and discussion precede each case report.

*Summary, Case 1.*—J. W., a newborn male, presented an unusual picture of severe hypoglycemia associated with pronounced and prolonged tendency to dehydration without diarrhea or vomiting. The hypoglycemia did not readily respond to the administration of subcutaneous or oral glucose. The rise of the blood sugar from 16.0 mg. per cent to 183 mg. per cent after administration of adrenalin is evidence that the hypoglycemia was not on the basis of depleted liver glycogen. A combination of pork adrenal cortex extract* and desoxycorti-

*"Pork adrenal cortex extract" contains 40 rat units per cubic centimeter. Each cubic centimeter is equivalent to 2 mg. of 17-hydroxy-11-dehydrocorticosterone (compound E) or 4 mg. of corticosterone. This extract is put up in oil. It was supplied through the courtesy of Dr. E. Gifford Upjohn of the Upjohn Company, Kalamazoo, Michigan.

costerone acetate adequately controlled the hypoglycemia and restored the electrolyte and water balance which was previously uncontrolled. The low serum sodium chloride of 66.7 milliequivalents per liter, obtained after frequent administration of normal saline subcutaneously, is presented as further evidence of a low adrenal cortical function.

The cerebral manifestations with subsequent mental retardation may possibly be due to the severe, prolonged hypoglycemia and associated anoxia during the early days of life.

CASE 1.—J. W., a two-day-old male infant, was admitted to St. Louis Children's Hospital Dec. 5, 1944. Birth weight was 2,800 Gm. In the forty-eight hours immediately following spontaneous delivery he was apparently normal. Periods of apnea and cyanosis then developed, which were relieved by carbon-dioxide inhalations, but the baby remained limp and unresponsive. C. W. B. T. glucose* was 5.0 mg. per cent. Spinal fluid was crystal clear but slightly xanthochromic. The skin was moderately jaundiced. The patient was given 10 per cent glucose intravenously and 5 per cent glucose in normal saline subcutaneously. Five hours later, twitchings of all extremities and irregular respirations occurred. Heart and lungs were negative, and blood pressure was 54 systolic. C. W. B. T. glucose later that day was still only 5.0 mg. per cent, despite intravenous and subcutaneous glucose. The patient was placed in an oxygen tent, 5 per cent glucose in normal saline was kept in the tissues constantly, and 10 per cent glucose offered by mouth every three hours. Twenty-four hours after the therapy, C. W. B. T. glucose was only 8.0 mg. per cent. One cubic centimeter of whole beef extract† was given immediately and 0.2 c.c. was given every four hours. On Dec. 9, 1944, C. W. B. T. glucose was 16 mg. per cent; 3 minims of adrenalin were given, and twenty minutes later C. W. B. T. was 183 mg. per cent. Periods of cyanosis became less marked, but occasional twitchings continued. Muscular tone improved, but marked tendency to diuresis developed. On December 11, true serum glucose was 5.0 mg. per cent; carbon-dioxide combining power was 58.5 volumes per cent; icterus, 28; nonprotein nitrogen 20 mg. per cent; total serum protein, 5.13 Gm.; serum calcium, 12.1 mg. per cent; serum phosphorus, 6.5 mg. per cent; total serum sodium chloride, 66.7 milliequivalents per liter. Urine was large in volume; specific gravity, 1.006; albumin, negative. Rothera, ferric chloride microscopic, and sugar tests were negative. Glucose was administered twice daily intravenously and subcutaneously. While the patient remained on whole beef extract every four hours there were fewer episodes of cyanosis and twitching, and blood sugars remained between 20 and 39 mg. per cent. When extract was withheld there was an increase in attacks of cyanosis and twitching, and associated lowering of blood sugar to between 5 and 15 mg. per cent. From Dec. 14 to Dec. 21, 1944, the infant's condition remained the same. The child was not gaining weight despite excessive amounts of subcutaneous and intravenous fluids. On December 19, daily injection of 1.0 mg. desoxycorticosterone acetate and 0.25 c.c. pork adrenal cortex extract† was begun. Immediately following this therapy, all twitching and cyanosis ceased. The patient was much less listless, blood sugars were maintained between 40 and 50 mg. per cent, and hydration was easily maintained without usual parenteral fluids. The total serum chloride rose to 106.1 milliequivalents per liter, and nonprotein nitrogen to 25 mg. per cent. When hormone therapy was stopped, blood sugar ranged between 10 and 20 mg. per cent and severe dehydration was evident.

When 1.0 mg. desoxycorticosterone acetate and 0.25 c.c. of pork adrenal cortex extract were resumed, the patient began to act and look like a normal infant, blood sugar became

*C.W.B.T. Capillary whole blood "true" glucose. This method utilizes the zinc sulphate—sodium hydroxide precipitating reagents of Somogyi and the sensitive Shaffer-Somogyi low blank reagent.

†Whole beef extract or adrenal cortex extract. Each cubic centimeter is obtained from not less than 40 Gm. of adrenal gland and contains not less than 50 dog units or 2.5 rat units. This extract is water soluble. It was supplied by the Upjohn Company.

elevated to normal, and hydration was restored. Starting Jan. 26, 1945, the adrenal hormones were gradually discontinued and blood sugars maintained between 65 and 70 mg. per cent. Weight on discharge was 3,800 Gm.

The patient was readmitted to the hospital at 7 months of age because of frequent transient episodes of generalized clonic convulsions of one month's duration. The child was mentally retarded, and could not hold his head erect or sit alone. Nonprotein nitrogen was 29.0 mg. per cent; carbon-dioxide combining power, 58 volumes per cent; total protein, 6.75 Gm.; sodium chloride, 93.1 milliequivalents per liter; blood sugar, 57.0 mg. per cent. On July 20, 1945, oral glucose tolerance and, on July 24, insulin tolerance were essentially normal.

*Summary, Case 2.*—L. P. presented a common and serious problem of protracted diarrhea beginning in the early days of life. Periods of acidosis and dehydration were frequent. An attack of several hypoglycemia was encountered, nearly resulting in death of the patient. After one month of accepted treatment without appreciable change in the condition, whole cortical extract was administered, which resulted in rapid improvement in the appearance of the baby and disappearance of diarrhea. After whole beef extract was stopped there was rapid loss of weight, but no reappearance of diarrhea. Hydration was immediately restored following desoxycorticosterone acetate administration. Pork adrenal cortex extract may have favorably influenced the blood sugar levels; however, one cannot be certain because of the short duration of the hypoglycemia. Unfortunately, blood electrolyte determinations were not done.

CASE 2.—L. P., a full-term, female, was born by spontaneous delivery Aug. 17, 1945. Birth weight was 3,800 Gm. She was well until the ninth day of life, when frequent watery stools and occasional vomiting began. Despite adequate parenteral therapy for a period of two weeks in a neighboring hospital, there was a steady decline and she was transferred to St. Louis Children's Hospital on September 25, at 6 weeks of age. The patient weighed 2,580 Gm., was markedly emaciated, dehydrated, very weak, and listless. There was no evidence of parenteral infection. Hemoglobin was 11.0 Gm., white blood cell count was 8,100 with normal differential. Carbon-dioxide combining power was 32.5 volumes per cent; and blood culture was sterile. Stool cultures showed a slow lactose fermenter of the colon group. The patient was given routine molar lactate therapy, and placed on one-third diluted, skimmed, evaporated milk. On October 24, after one month's hospitalization with no appreciable improvement, the infant suddenly became apneic and gray, and was in a state of collapse. C. W. B. T. glucose during this episode was 6.0 mg. per cent. Five minims of adrenalin were given subcutaneously and in one-half hour the C. W. B. T. glucose was 65.0 mg. per cent, and the patient was much improved. Daily injection of 2.0 c.c. whole beef adrenal cortical extract was begun. Single urine specimens contained large amounts of chlorides. Two days following therapy there was obvious improvement in stools; the patient was stronger, more alert, took food better, and began to gain weight without parenteral fluids. Urine contained only traces of chlorides when diarrhea subsided. When the adrenal hormone therapy was begun, weight was 2,560 Gm.; four days later it was 2,960 Gm. Five days after therapy, diarrhea had completely disappeared for the first time since the age of 9 days. On October 31, C. W. B. T. glucose was 71.0 mg. per cent. On October 28, whole beef extract was discontinued, and 0.25 c.c. pork adrenal cortex extract given intramuscularly every other day. Nonprotein nitrogen was 41.0 mg. per cent, and carbon-dioxide combining power 50 volumes per cent on October 30. After change to pork adrenal extract, blood sugar remained normal and diarrhea did not reappear, but there was a rapid weight loss to 2,560 Gm. by October 31. December 1, daily injections of 2.0 mg. desoxycorticosterone acetate were begun. Three days later weight had risen to 2,820 Gm. without visible evidence of edema. Desoxycorticosterone acetate was discontinued on December 12, and the patient was

discharged December 24 weighing 2,800 Gm. Caloric intake was then gradually increased without recurrence of diarrhea, and on Jan. 3, 1946, weight was 4,000 Gm. When last seen, at 9 months of age, the child was found to be perfectly normal.

*Summary, Case 3.*—L. Y., a female premature infant, developed anorexia, steady weight loss, and frequent periods of dehydration despite adequate parenteral therapy. No gastrointestinal disturbances were noted. An attack of hypoglycemia was immediately relieved by intravenous glucose. After administration of pork adrenal cortex extract and desoxycorticosterone acetate, prompt clinical improvement was evidenced, hydration was restored, and clinical manifestations of hypoglycemia did not reappear. Death was caused by aspiration of milk. Post-mortem examination was denied.

CASE 3.—L. Y., a two months premature, female infant was born Dec. 8, 1944. Birth weight was 1,600 Gm. There was an uncomplicated delivery, spontaneous cry, and normal birth. She was admitted to St. Louis Children's Hospital at 13 days of age because of gradual weight loss and anorexia. There was no history of diarrhea or vomiting. The patient was listless, dehydrated, and weighed 1,180 Gm. Temperature was 34.6° C.; Hemoglobin, 11.2 Gm.; red blood cell count, 3.71 million; white blood cell count, 17,250; normal differential count. Kahn test was negative. The infant was given routine premature care and penicillin, 5,000 units every three hours. She was much improved shortly after entry, but twenty-four hours later was found to be cyanotic, apneic, and in state of collapse. C. W. B. T. glucose was 10.0 mg. per cent; after intravenous injection of 10 per cent glucose, and 5 per cent glucose in normal saline subcutaneously, active cry and normal color returned. Following this episode, 2.0 mg. desoxycorticosterone acetate and 0.25 c.c. of pork adrenal cortex extract were administered intramuscularly. Twenty-four hours later the patient was much better hydrated, more active, and appeared to be well on the way to recovery. The pork adrenal cortex extract and 0.5 mg. desoxycorticosterone acetate were administered again the following day. Two days after onset of therapy the weight was 1,310 Gms. The next day the patient vomited, aspirated milk, and choked to death. No post-mortem examination was obtained.

*Summary, Case 4.*—M. G., a premature infant, developed a staphylococcus septicemia and urinary infection during the course of a severe diarrhea. The sepsis was readily controlled by the use of penicillin and sulfadiazine. Following the eradication of the infection, periods of unexplained dehydration and attacks of hypoglycemia developed. These episodes were associated with collapse and extreme listlessness. After two days of adrenal hormone therapy, there was no return of the hypoglycemia; marked improvement in the diarrhea was noted, resulting in an increased appetite, better hydration, and a more vigorous baby. It was felt that the diarrhea and the transient sepsis probably added greatly to the demands made on the physiologically low functioning adrenal cortex. These demands could not be promptly met, and because of probable poor intestinal absorption of glucose, possible lack of liver glycogen or poor mobilization, hypoglycemia resulted. Administering adrenal steroids was seemingly sufficient to meet the increased need for circulating hormones and tide the infant over this critical period.

CASE 4.—M. G., a female twin, was born by spontaneous delivery, three weeks premature, on Dec. 5, 1944, with a birth weight of 2,320 Gm. On the fourth day of life watery stools developed, followed by a rapid loss of weight despite adequate parenteral therapy. When

seven days old, she was admitted to St. Louis Children's Hospital, weighing 2,070 Gm. Both eardrums were slightly thickened and the skin was dehydrated but the infant was fairly alert and hungry. The carbon-dioxide combining power was 37 volumes per cent; blood and stool cultures were negative. Kahn and tuberculin tests were negative. Usual amounts of parenteral fluids and sulfadiazine therapy were begun, and the next few days there was some improvement in the diarrhea. December 29 diarrhea suddenly became worse; vomiting commenced, and periods of unexplained listlessness and collapse followed. Blood culture grew out a few colonies of *Staphylococcus aureus*, and growth of *Bacillus coli* was cultured from the urine, although the blood-sulfadiazine level was 8.9 mg. per cent. Penicillin, 5,000 units every three hours, was administered, and subsequent blood cultures were sterile. Despite improvement in the diarrhea and disappearance of parenteral infection, periods of collapse, extreme listlessness, and dehydration continued. On January 3, the spinal fluid was found to be crystal clear, Pandy reaction negative, 3 cells. The spinal fluid glucose was 10.0 mg. per cent, C. W. B. T. glucose taken the same day about two hours after feeding was 29.0 mg. per cent. January 5, the C. W. B. T. glucose was 10.0 mg. per cent, and 2 minims of adrenalin were given subcutaneously between feedings for twenty-four hours. The following day, daily injections of 0.25 c.c. pork adrenal cortex extract and 0.5 mg. desoxycorticosterone acetate were instituted. In next two days there was little change, and C. W. B. T. glucose ranged from 5.0 mg. per cent to 25.0 mg. per cent. By January 9, there was a decided improvement. The patient became more alert and eager to feed, and no further periods of listlessness, dehydration, or collapse were noted. The blood sugar ranged from 40 to 77 mg. per cent. The blood pressure rose from 70/40 systolic to 98/60. The pork adrenal extract and desoxycorticosterone acetate were gradually discontinued without recurrence of symptoms. The infant was discharged January 25, weighing 2,340 Gm. Growth and development have been normal.

*Summary, Case 5.*—The illness of K. S., a female premature infant, began with frequent attacks of convulsions the first few days of life, followed by a failure to gain weight. At first, response was favorable to routine premature care, but she later developed anorexia, moderate number of loose stools, and a pronounced tendency to dehydration. Staphylococcus septicemia developed, and later a localized abscess of the back was incised. The infection promptly responded to penicillin therapy, but loose stools continued, and the patient appeared to be slowly dying. After administration of desoxycorticosterone acetate there was a rapid improvement in hydration, disappearance of the diarrhea, and return of pink color and normal activity. She has subsequently remained well.

CASE 5.—K. S., a female, premature infant, one of identical twins, was born Aug. 31, 1944, after normal delivery. Birth weight was 1,820 Gm. She had a history of cyanosis at birth and frequent attacks of generalized twitchings the first few days. She was admitted to St. Louis Children's Hospital on September 9 because of failure to gain weight. Weight was 1,500 Gm. She was active, had good color and no evidence of infection. Physical examination was essentially negative. The infant did well on the usual premature routine, and by September 27, her weight had increased to 2,320 Gm. Then there was a gradual loss of appetite, occurrence of loose stools, and weight decrease to 1,860 Gm. by October 4. She began to vomit all feedings. The usual therapy of parenteral fluids, intravenous glucose, blood transfusion, vitamins, and sulfadiazine was given. On October 5, blood culture grew out *Staph. aureus.* Urine was clear. Four days later a localized abscess of back was found, incised, and drained. Pus from the abscess also cultured out *Staph. aureus.* Penicillin in addition to sulfadiazine was given, and a few days later the back had completely healed, and blood cultures became sterile. Despite the eradication of all known infection, the patient showed little improvement, requiring frequent subcutaneous fluids to maintain hydration; the stools continued to be loose but not frequent. On November 4, the assistant Resident noted: "The baby looks as though it is dying of old age." Skin was atrophic,

dehydrated, and slightly icteric. On November 5, 2.0 mg. desoxycorticosterone acetate were given. Twenty-four hours later the baby looked better; color and appetite improved. Desoxycorticosterone acetate, 0.5 mg., was given daily. On November 7, the infant began to cry hungrily between feedings, and stools were more formed. On November 4, the weight was 1,880 Gm. and by November 10, it had risen to 2,240 Gm., without parenteral fluids. Desoxycorticosterone acetate was continued through November 20, and then gradually stopped. The patient was discharged December 5, weighing 2,760 Gm. Reports from the mother indicate normal growth and development at 9 months of age.

*Summary, Case 6.*—A. S., identical twin of Case 5, presented a similar history. She also developed loose stools and was very difficult to keep hydrated. The patient's condition differed from that of her twin in two respects only; first, there was no definite evidence of infection; secondly, hypoglycemia symptoms developed. This infant did not receive desoxycorticosterone acetate; otherwise, the treatment was identical in the two cases. Post-mortem examination showed very little other than a small patch of terminal bronchopneumonia. The slight cirrhosis of the liver may have been a factor in the development of the hypoglycemia. The endocrine organs were said to have been normal for a premature infant.

CASE 6.—A. S., was a female, identical twin, whose sister was admitted to the hospital at the same time. Born Aug. 31, 1944, her birth weight was 2,200 Gm. She had a history of cyanotic attacks and generalized twitchings the first few days. She entered St. Louis Children's Hospital Sept. 9, 1944, because of failure to gain weight. Her weight was 1,350 Gm. The infant was weak and listless, but had good color and physical examination revealed no abnormalities. There was no evidence of infection. Kahn test was negative. She was given identical premature care to that of her twin. By September 29, her weight had increased to 1,650 Gm. From this time on, a few loose stools were noted, and weight dropped to 1,560 Gm. within a few days. Her skin became slightly icteric, turgor poor, and she became dehydrated and listless. Frequent administration of subcutaneous fluids and blood transfusions were necessary. October 20, the infant became stiff and pale. Blood calcium was 12.5 mg. per cent, and nonprotein nitrogen, 28 mg. per cent. Following intravenous glucose, there was definite improvement. The serum glucose was 15.0 mg. per cent. On October 27, there was definite jaundice evident, and icterus index was 61.0 mg. per cent. Nonprotein nitrogen was 29.0 mg. per cent; total proteins, 5.5 gm.; and serum glucose, 17.0 mg. per cent. Blood cultures were sterile. Sulfadiazine and penicillin therapy were begun. On Oct. 30, 1944, the carbon-dioxide combining power was 31.6 volumes per cent, serum glucose, 54.0 per cent, and non-protein nitrogen, 29.0 mg. per cent. Loose stools continued and hydration was very difficult to maintain. By November 2 she was less jaundiced. Icterus index was 20 mg. per cent, but the baby remained weak, took formula poorly, and would dehydrate rapidly despite frequent administration of fluids. On November 3, her respiration was shallow and color gray. Intravenous glucose resulted in immediate crying and improvement in color, and the patient remained improved until three hours later when she was found gasping and failed to respond to emergency measures. She expired November 3. Necropsy revealed slight cirrhosis of the liver and slight generalized icterus of all organs. The only evidence of infection was a small patch of terminal bronchopneumonia. All other organs of the body were normal for a premature infant.

*Summary, Case 7.*—B. S., a full-term infant, had a severe physiologic icterus and later developed protracted diarrhea associated with periods of acidosis and a marked tendency to dehydration, despite frequent administration of parenteral fluids. Three weeks after entering the hospital the baby was emaciated and

listless, and there was no significant improvement in diarrhea. Improvement in hydration, number of stools, and general well-being of the infant was noted following the administration of desoxycorticosterone acetate. Here again, it is felt that supplying the cortical steroid during this critical period was sufficient to take care of extra demands that could not be met by the patient's adrenal glands.

CASE 7.—B. S., a full-term female infant, was born May 11, 1945, with spontaneous cry and respiration. Birth weight was 2,900 Gm. The patient was reported slightly jaundiced at birth. Progressive increase in icterus was noticed. Mother, father, and baby were all found to be Rh positive. The infant was admitted to the St. Louis Children's Hospital June 13, 1945, with a weight of 2,800 Gm. The child was active, well developed, and nourished. Skin and sclerae were very jaundiced. Kahn test was negative; hemoglobin, 17.4 Gm.; red blood cell count, 4.5 million; urine, negative. By June 17 the icterus was diminishing. The course was uneventful until June 21, when vomiting and loose stools developed, resulting in a marked weight loss. Routine parenteral therapy, plus penicillin, 5,000 units every two hours, was begun. There was no evidence of infection. The diarrhea persisted with frequent periods of acidosis. June 23, the C. W. B. T. was 105 mg. per cent. Large amounts of parenteral fluids and intravenous glucose were required to maintain hydration. July 4, three weeks after entry, her weight was 2,340 Gm. and there was no significant improvement. An initial dose of 2.0 mg. desoxycorticosterone acetate was given, then 0.5 mg. daily for the following three days. Prompt hydration and general improvement in the color, appetite, and activity were noted. By July 7, stools were much improved; serum sodium chloride was 120.0 milliequivalents per liter, glucose was 61.5 mg. per cent, and nonprotein nitrogen, 27.6 mg. per cent. Weight rapidly increased from 2,340 Gm. to 2,580 Gm. four days later, and parenteral fluids were no longer required. The patient continued to improve after desoxycorticosterone acetate was discontinued. She was discharged July 14 weighing 2,760 Gm. The child has remained well.

*Summary, Case 8.*—G. T., a male infant, entered the hospital at 3 weeks of age because of failure to gain weight. There was a history of convulsions during the early days of life. A urinary infection was found, which readily cleared after penicillin and chemotherapy. After three weeks of constant care, the appetite remained poor, and the infant continued to be listless. Hydration was maintained only by daily administration of parenteral fluids. These symptoms, plus a moderately low serum sodium chloride, elevated nonprotein nitrogen, absence of free hydrochloric acid of the stomach, and a peculiar "dirty" pigmentation of the skin, suggested possible hypofunction of the adrenal cortex. The rapid improvement following desoxycorticosterone acetate therapy strengthened this impression. It is of interest to note that the patient got along well at home for one month on the addition of table salt to the formula, but later required desoxycorticosterone acetate again. Before therapy was started, it was found that the sodium was low and potassium definitely elevated. Following desoxycorticosterone acetate therapy, the sodium and potassium levels returned to normal, and the patient progressed normally.

The determination of urinary steroids ruled out the possibility of an androgenic hyperplasia associated with hypofunction of the "true" cortex.[3] There has been no evidence suggesting adrenal tumor, although pyelograms have not been done. This is the first and only case in this series requiring prolonged hormone therapy. The patient at present requires daily injections of de-

soxycorticosterone acetate; therefore, one cannot be certain whether or not this is a case of physiologic low activity of the adrenal cortex. In experimental animals, the prolonged administration of cortical hormones may lead to atrophy of the adrenal gland. This possibility must also be considered, provided it remains necessary to continue the injections of desoxycorticosterone acetate.

CASE 8.—G. T., a three-week-old male, was born April 12, 1945, after a normal, uncomplicated delivery. Birth weight was 3,180 Gm. The baby appeared normal after birth with the exception of underdeveloped genitalia; the testes were undescended, and there was a hypospadias. On the second day of life, generalized convulsions, periods of apnea, and cyanosis developed. Following this, the infant lost weight steadily and appetite remained poor. Urinalysis one week before admission showed many pus cells, albumin, and bacteria. Stools were normal and there was no vomiting. He entered St. Louis Children's Hospital May 3 because of weight loss. A small, thin, malnourished infant, he weighed 2,660 Gm. Physical examination was essentially negative with the exception of the penis, which was small and hung as if bound down to undeveloped scrotum. Urine contained 50 to 60 pus cells per low power field, one plus albumin, *Bacillus coli* and few staphylococci. Penicillin and sulfanilamide were started, and in a few days the urine was completely cleared. On May 4, nonprotein nitrogen was 49.5 mg. per cent, carbon-dioxide combining power was 60.8 volumes per cent, calcium, 11.8 mg. per cent, phosphorus 7.4 mg. per cent, blood culture, sterile. May 24, three weeks later, there had been no weight gain; the patient was listless and nursed poorly. Daily parenteral fluids were required to prevent dehydration. There was no evidence of infection since the transient pyuria. On May 30, when first seen through the courtesy of Dr. J. V. Cooke, the patient appeared chronically ill. There was a peculiar "dirty gray" pigmentation of the skin. Blood pressure was 80 systolic, which is low for the cuff used. Nonprotein nitrogen was 59.0 mg. per cent, carbon-dioxide combining power was 57 volumes per cent, and total serum sodium chloride, 86.7 milliequivalents per liter. Gastric analysis showed no free hydrochloric acid. C. W. B. T. glucose was between 77 mg. per cent and 84 mg. per cent. On May 31, 1945, daily doses of 1.0 mg. desoxycorticosterone acetate were started. Three days later, the patient was obviously more active and his appetite improved. Weight before hormone therapy was 2,625 Gm. An average of 250 c.c. of subcutaneous fluids was required daily to prevent weight loss. June 11, after 1.0 mg. desoxycorticosterone acetate had been given for eleven days, no parenteral fluids were required, and there was a steady gain in weight to 2,855 Gm. Desoxycorticosterone acetate was discontinued June 11. The patient continued to improve and was discharged July 3 weighing 3,100 Gm. The mother was instructed to put 3.0 Gm. of table salt in the total day's formula. Seen again August 16, weight was 4,800 Gm., but the "dirty gray" skin color was still present. Blood pressure was 94/60; serum sodium chloride, 97.5 milliequivalents per liter; nonprotein nitrogen, 37.5 mg. per cent. Urine was clear and strongly positive for chlorides. On Aug. 21, 1945, the patient was readmitted to the hospital because of sudden onset of anorexia, vomiting, and loose stools of two days' duration. His weight was 4,540 Gm., he was irritable, listless, and moderately dehydrated. There was no evidence of infection. The patient was given parenteral fluids and started on formula with 3.0 Gm. table salt added. Aug. 24, 1945, serum glucose was 78 mg. per cent; nonprotein nitrogen, 35.5 mg. per cent; carbon-dioxide combining power, 43.5 volumes per cent; and serum sodium chloride, 88.6 milliequivalents per liter. The patient ate poorly and required frequent administration of subcutaneous fluid, despite cessation of vomiting and diarrhea. September 3 while on 3.0 Gm. of table salt in formula, the total serum sodium chloride was 98.4 milliequivalents per liter; sodium, 130.9 milliequivalents per liter; and potassium, 10.2 milliequivalents per liter. September 4, weight was 4,330 Gm. The next day, desoxycorticosterone acetate was begun and parenteral fluids discontinued. A dose of desoxycorticosterone acetate varied from 1.0 to 2.0 mg. There was a gradual increase in weight, and by Sept. 27, 1945, when the steroid was discontinued, the weight was 4,925 Gm. The patient continued to look well, but there was a slow, steady loss

of weight. On October 6, daily doses of 5.0 mg. desoxycorticosterone acetate were begun. The patient was discharged three days later. Urine was collected for steroid determination. Dr. Willard Allen's note read: "The total urinary steroids and the 17 ketosteroids are both below 1.0 mg. per day. This indicates that there is no adrenal hyperfunction insofar as the androgens are concerned." The patient was seen again November 4. During this interval he received daily injections of 5.0 mg. desoxycorticosterone acetate and 3.0 Gm. sodium chloride in each day's formula. Weight was 7,020 Gm., and there was no evidence of edema. The patient was normal in every respect. Blood pressure was 92/60; heart, normal; serum sodium chloride, 104.4 milliequivalents per liter; sodium, 143.1 milliequivalents per liter; potassium, 6.9 milliequivalents per liter. Desoxycorticosterone acetate was then given every other day and by Jan. 3, 1946, his weight was 7,900 Gm., with the skin pigmentation barely noticeable. Desoxycorticosterone acetate was discontinued entirely. Immediate failure of appetite and rapid weight loss ensued. The patient still requires 2.0 to 3.0 mg. desoxycorticosterone acetate daily, but an attempt is being made to gradually reduce the dosage.

*Summary, Case 9.*—S. D., a full-term male, developed disturbance of gastrointestinal function in the early days of life. The repeated bouts of diarrhea, vomiting, and inability to gain weight remained essentially unaltered, despite everything that could be done over a period of two and one-half months' hospitalization. Within a short period following administration of adrenal cortex extract, the stools became normal, and appetite increased. Despite the development of an extensive virus pneumonitis, the diarrhea did not recur while the patient was on extract. There was no appreciable gain in weight until desoxycorticosterone acetate was given daily. A most interesting finding was that of low trypsin activity before prolonged hormone therapy and a return to normal after treatment. The skin discoloration was very similar to that of the patient in Case 7.

Case 9.—S. D., a full-term male, was born June 29, 1945, by spontaneous delivery, and was apparently normal except for loose stools, averaging eight or nine per day. During the first three weeks of life there were frequent periods of vomiting, and just before entering the hospital, stools became more frequent. The patient was admitted to the hospital August 18. He was gray, markedly dehydrated, and very listless; the fontanelle was sunken and the heart was small. Genitalia were normal. There was no evidence of parenteral infection. Urine was clear and alkaline in reaction. Nonprotein nitrogen was 62 mg. per cent, blood culture, sterile. The infant was given 10 per cent glucose intravenously, fortified lactate Ringer's subcutaneously, blood transfusions, and parenteral vitamins. On August 20, carbon dioxide was 64.4 volumes per cent. Two months later there was little change in the patient's condition. October 20, Dr. A. F. Hartmann's note read: "Patient began to vomit in early infancy, then developed diarrhea and has continued to have diarrhea with but short periods of remission." On October 29, carbon dioxide was 62 volumes per cent; nonprotein nitrogen, 41.0 mg. per cent; and serum glucose, 60.1 mg. per cent. The patient gradually lost ground. Weight was 2,840 Gm., only 40 Gm. above that on admission two and one-half months previously. Skin was a "dirty gray" in appearance. October 29, when I first saw the patient through the courtesy of Dr. Hartmann, daily injections of 5.0 c.c. of whole beef adrenal extract were begun. The following day the patient was fairly alert and cried for food, and oxygen tent was no longer required. He was kept on food by mouth despite loose stools. Five days after adrenal hormone therapy, stools were almost normal, appetite decidedly increased, and weight increased to 4,020 Gm. without the large amounts of parenteral fluids formerly required to maintain hydration. Thirteen days after hormone therapy, on Nov. 15, 1945, there had been ten days of normal to constipated stools, with no parenteral fluids necessary and an appetite which improved

steadily. November 16, there was sudden elevation of temperature, weight loss to 3,460 Gm. and skin dehydration, but no vomiting or return of diarrhea. Urine samples contained large amounts of chlorides. The fluoroscopic examination showed extensive infiltration in the right lung. White blood cell count was 4,980; stab cells, 4; segmented cells, 18; lymphocytes, 77; and monocytes, 11. A diagnosis of atypical pneumonia was made. Penicillin, 5,000 units every three hours, was started. The temperature subsided rapidly. Because of pronounced tendency to dehydration with onset of infection, the whole adrenal gland extract was discontinued, and a daily dose of 5.0 mg. desoxycorticosterone acetate was started. Within six days weight increased from 3,400 Gm. to 4,300 Gm., and appetite returned to normal. By November 21, desoxycorticosterone acetate was administered every other day and weight dropped to 3,750 Gm. On November 29, daily doses of desoxycorticosterone acetate were resumed, resulting in a steady weight gain and general improvement and December 8, weight was 4,520 Gm. Six days later desoxycorticosterone acetate was discontinued and the patient remained well. December 5, the serum sodium chloride was 95.8 milliequivalents per liter. The patient was discharged Dec. 19, 1945, weighing 4,880 Gm.

On November 8, Dr. Gilbert Forbes had examined the duodenal juice for "trypsin activity" and found a marked decrease. December 17, after desoxycorticosterone acetate therapy, this examination was repeated, and normal tryptic activity was found. The patient continued to do well and on Jan. 23, 1946, weighed 6,590 Gm.

## DISCUSSION AND SUMMARY

There has been relatively little investigation of the activity of the adrenal cortex during the early days of life. Bruch and McCune[19] made a biochemical investigation into the physiologic significance of involution of the adrenal glands in newborn infants. They could not demonstrate blood chemical changes similar to those seen in Addison's disease.

Miller[20] demonstrated that the blood sodium level rose after the first few days of life. He states that the low values may be interpreted as either evidence of shock or adrenal insufficiency. He also showed that the physiologic weight loss, which averages 6.5 to 7.8 per cent in newborns, was reduced to an average of 4.5 per cent after the administration of desoxycorticosterone acetate. Miller suggests that adrenocortical insufficiency may be another factor producing the physiologic weight loss.

Collis[21] in his paper, "Premature Infant's Management and Prognosis," wrote a brief paragraph recommending adrenal extract for relief of dehydration with ketosis in premature infants. No further statement was made. On the other hand, Young and associates[22] in their investigation of renal function of premature infants, suggested that a low glomerular filtration rate combined with an overactive suprarenal cortex might account for the very low mineral clearances. They were, however, unable to explain the low potassium clearances on this basis. Akerren[23] in his excellent paper, "Shock in Premature Children," states that Cortin has had a favorable effect on the debilitated infant. No details were presented.

The use of biochemical changes alone to rule out hypofunction of the adrenal cortex has its limitations, particularly when we realize that infants have much lower renal mineral clearances the first few weeks of life than at any other time.[22] The electrolyte picture of the blood may be perfectly normal in some cases of Addison's disease and in adrenalectomized animals. The flooding of the

fetus with estrogenic hormones from the placenta, plus the low renal mineral clearance of the newborn and premature infant may be the reason why it has been difficult to demonstrate blood chemical changes suggesting hypofunction of the adrenal cortex.

During most of the intrauterine period the true cortex remains as a thin rim of closely packed cells with deeply stained nuclei. The X zone, fetal cortex, or androgenic zone, comprises the largest part of the adrenal gland, and grows rapidly during the intrauterine period. It seems likely that because of the unusually small amount of the true cortical tissue, the fetus does not rely entirely on the secretions of hormones from this tissue for its rapid growth and development. Immediately following birth, the androgenic tissue involutes, and there is most likely an increased need for secretion of hormones from the true cortex. This demand increases from day to day, and, as a result, there is a corresponding enlargement in size of this tissue during the first four weeks.[24, 25] During this adjustment period could not there be a physiologically low activity of the true cortex? This concept, if true, could explain the reason for many deaths in premature and full-term infants the first few weeks of life, which are preceded by periods of unexplained and prolonged debility not responding to treatment. It would also answer a question which has puzzled physicians for many years, namely, why do certain infants fail to recover following various diseases contracted during early life, despite the complete eradication of the infection? The most recent investigations[1, 26, 27] have shown that there is a physiologic hypoglycemia during the first few days of life which may be explained by a lack of adrenal cortical or anterior pituitary secretions, physiologic hyperinsulinism, immature liver, or a combination of these. The hypoglycemia might be interpreted as a disturbance in carbohydrate metabolism secondary to low adrenal function. The rapidity with which glycogen disappears in the newborn liver after fasting is also suggestive of low cortical function. Rushton and associates[28] reported a case of an adult who had severe attacks of hypoglycemia without signs or symptoms of Addison's disease. Post-mortem examination revealed the adrenal glands to be markedly atrophic.

Himwich[29] has shown that in newborn infants and young animals the cerebral metabolism is very low. He and others have emphasized that the foremost antagonist to the parasympathetic-insulin apparatus is the sympathetic adrenal system which is "probably functioning poorly or not at all in the newborn the first few days of life." Adrenalin has been demonstrated in the adrenal medulla of animal fetuses, however "the human fetal medulla seems almost without its presence."[30] Recently Vogt[31] in investigating various conditions affecting the rate of hormone output by the suprarenal cortex, demonstrated that through adrenalin the sympathetic nervous system has an indirect control over the activity of the adrenal cortex. If the sympathetic adrenal system is functioning poorly in newborns the first few days of life, even though there were small amounts of the cortical hormone present, it may not be available when most needed.

Each of the cases reported here may present some phase of hypofunction of the adrenals. The patients treated were those which showed little hope of recovery, and any therapeutic measures which had the slightest chance of benefitting the patient were justified, no matter how drastic. It is difficult to portray the critical state of these patients and the dramatic improvement following hormone therapy.

With the exception of Cases 2 and 3, the patients were observed for from three to ten weeks in the hospital, with no demonstrable improvement in their conditions before hormone therapy was started.

The characteristics common to every infant described here are: general debility and weakness, appearance of impending shock, and marked tendency to dehydration, in spite of adequate parenteral fluid therapy. In addition to these signs, five of the nine patients (Cases 1, 2, 3, 4, and 6) had superimposed attacks of hypoglycemia that were immediately relieved by elevation of the blood sugars. Although it is well known that blood sugars may be extremely low in thriving premature infants,[32] the symptoms of collapse associated with low blood sugars, the immediate improvement after intravenous glucose, and the failure of return of these symptoms during periods of elevated blood sugar levels would be difficult to explain on the basis of physiologic hypoglycemia.

Two patients (Cases 1 and 3) had no evidence of infection or gastrointestinal disturbances. Four patients (Cases 2, 6, 7, and 9) had anorexia and loose stools from the early days of life without evidence of infection. One patient (Case 8) had a transient urinary infection without gastrointestinal disturbances other than anorexia. Two patients (Cases 4 and 5) with diarrhea developed staphylococcus septicemia readily responding to penicillin, but loose stools continued, and downhill course persisted until hormone therapy was started.

In addition to the cases listed above, over a period of three years at least a dozen premature infants have been observed who have shown prompt and beneficial response to the administration of whole adrenal extract (Upjohn's "adrenal cortex extract") in dosage of 1.0 c.c. per kilo body weight per day, given subcutaneously. Almost without exception improvement was noted within two to three days of the injection and was indicated by increased appetite, maintenance of hydration without parenteral fluids, and a more vigorous baby. The therapy was continued on the average of seven days and then stopped with no discernible relapses.

The daily dosage of desoxycorticosterone acetate varied from 0.5 to 5.0 mg., depending upon the clinical response. These are relatively large doses of adrenal steroids, compared to those required in the regulation of Addison's disease in adults. The tissues of early infancy may fail to completely absorb the oil, and it is sometimes difficult to be certain all of the injection is given into the muscle. Another explanation for the necessity for large doses is the possibility that this is not a replacement therapy after all, but rather a nonspecific action of the steroids. Possibly, if regulated amounts of electrolytes are given by mouth the effective doses of desoxycorticosterone acetate may be lowered.

Although no harmful effects have been noted from the administration of the adrenal hormones, with the possible exception of Case 8, a warning should be given against the promiscuous use of desoxycorticosterone acetate. Experimental and clinical observations[33, 34] have definitely shown that when excessive doses of desoxycorticosterone acetate are used with large amounts of sodium chlorides, degenerative lesions in the arterioles of the brain, kidneys, and heart, may result. Because of the physiologically low renal activity during early life, this steroid may cause further depression of this function. It is also theoretically possible to cause atrophy of the adrenal cortex following unwarranted and prolonged administration of this hormone. Because of our limited knowledge of the potent extracts and the possibly dangerous effects upon the patient, it is suggested that under no circumstances should they be used until further investigations have been made by institutions where the patient can be closely studied. Hormone therapy may, in the future, play an intergral part in the maintenance of fluid and electrolyte balance in selected cases during early infancy. It is realized that a great deal of research will be required to prove the validity of the concept outlined herein. Further clinical and biochemical investigations are in progress.

## CONCLUSIONS

1. A theory of physiologic hypofunction of the adrenal glands during the early weeks of life has been presented. Anorexia, failure to gain weight, unexplained tendency to dehydration, attacks of hypoglycemia and protracted diarrhea; one or more of these signs or symptoms originating in the neonatal period and not responding to treatment should be considered as possible manifestations of low adrenal cortical function. These patients may be benefited by hormone therapy.

2. The cases recorded here present a variety of symptoms which are interpreted as signs of low adrenal function. These symptoms rapidly subside after the administration of adrenal cortical hormones. No harmful effects from the injections were encountered.

3. Adrenal hormone therapy may be a necessary adjunct in the maintenance of proper water and electrolyte balance, the preservation of normal intestinal function and the adjustment of a deranged carbohydrate metabolism in selected patients during early infancy.

4. Hypoglycemia during early infancy is not a rare occurrence and it is not uncommonly associated with symptoms of shock.

5. It appears that pork adrenal extract prevents the reappearance of severe hypoglycemia during early infancy.

## REFERENCES

1. Hartmann, A. F., and Jaudon, J. C.: J. PEDIAT. 11: 1, 1937.
2. Butler, A. M., Ross, R. A., and Talbot, N. B.: J. PEDIAT. 15: 831, 1939.
3. Wilkens, L., Fleishman, W., and Howard, J. C.: Endocrinology 26: 385, 1940.
4. Thelander, H. E., and Cholffin, M.: J. PEDIAT. 18: 779, 1941.
5. Jaudon, J. C.: J. Clin. Endocrinol. 6: 558, 1946.
6. Loeb, R. F.: Science 76: 420, 1932.
7. Jaudon, J. C.: J. PEDIAT. 28: 737, 1946.

8. Althausen, T. L., Anderson, E. M., and Stockholm, M.: Proc. Soc. Exper. Biol. & Med. **49:** 342, 1939.
9. Wilbrandt, W., and Ling-Yel, L.: Bioch. Z. **204:** 267, 1933.
10. Dennis, C., and Wood, E. H.: Am. J. Physiol. **139:** 182, 1940.
11. Clark, W. C.: Proc. Soc. Exper. Biol. & Med. **40:** 468, 1939.
12. Harrison, H. E., and Darrow, D. C.: Am. J. Physiol. **125:** 631, 1939.
13. Swingle, W. W.: Physiol. Rev. **24:** 1940.
14. Tuerkischer, E., and Wertheimer, E.: J. Endocrinol. **4:** 143, 1945.
15. Thaddea, S.: Med. Klin. **32:** 49, 1936, and **36:** 76, 1936.
16. Cori, F., and Cori, G. T.: J. Biol. Chem. **74:** 473, 1927.
17. Britton, S. W., and Silvette, H.: Am. J. Physiol. **100:** 693, 1932, and **118:** 594, 1937.
18. Long, C. H., Kapzin, B., and Fry, E.: Endocrinology **26:** 309, 1940.
19. Bruch, H., McCune, D. J.: Am. J. Dis. Child. **52:** 863, 1936.
20. Miller, R. A.: Arch. Dis. Childhood **16:** 230, 1941.
21. Collis, W. R. F.: Brit. Med. J. **1:** 31, 1944.
22. Young, W. F., Hallum, J. L., and McCance, R. A.: Arch. Dis. Childhood **16:** 243, 1941.
23. Akerren, Y.: Acta Paediatrica **32:** 804, 1945.
24. Grollman, A.: The Adrenals, Baltimore, 1936, Williams & Wilkins.
25. Benner, M. C.: Am. J. Path. **16:** 793, 1940.
26. McKittrick, J. D.: J. PEDIAT. **16:** 151, 1940.
27. Ketteringham, R. C.: Am. J. Dis. Child. **59:** 542, 1940.
28. Rushton, J. G., Cragg, R. W., and Stalker, L. K.: Arch. Int. Med. **66:** 531, 1940.
29. Himwick, H.: Am. J. Digest Dis. **11:** 1, 1944.
30. Smith, Clement A.: The Physiology of the Newborn Infant, Springfield, Ill., 1945, Charles C. Thomas, p. 268.
31. Vogt, M.: Am. J. Physiol. **103:** 317, 1944.
32. Van Creveld, S.: Am. J. Dis. Child. **38:** 912, 1929.
33. Selye, H., Beland, E., and Sylvester, O.: Exper. Med. & Surg. **2:** 224, 1944.
34. Forster, F. M., Cantarow, A., Herbut, P. A., Paschkis, K. E., and Rakoff, A. E.: J. Clin. Endocrinol. **6:** 77, 1946.

# INTRA-ARTICULAR PENICILLIN TREATMENT OF SUPPURATIVE ARTHRITIS IN INFANTS AND CHILDREN

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ALTHOUGH local treatment of suppurative arthritis with penicillin has been advocated,[1-5] we have been unable to find any detailed reports of such therapy in infants and children; three cases thus treated were briefly mentioned by Herrell and Kennedy[6] in a report on the use of penicillin in pediatrics. The paucity of data prompted this report of four cases of pyarthrosis treated by intra-articular penicillin on the Pediatric service of the New York Hospital between November, 1944, and January, 1946.

## CASE REPORTS

CASE 1.—M. P., a newborn, white female infant, was admitted on Oct. 22, 1944, because of an imperforate anus. Multiple gastrointestinal and genitourinary anomalies were found at operation. On the tenth postoperative day the temperature rose to 38.2° C. and the white cell count was 55,000 with 92 per cent polymorphonuclear cells. Examination disclosed moderate purulent drainage from a cut-down site in the ankle. Blood, nose, throat, and ankle cultures showed a hemolytic *Staphylococcus aureus*. Intramuscular penicillin (10,000 units every three hours, doubled after five days) and sulfadiazine (0.2 Gm. per kilogram per day) were started on the eighteenth postoperative day. After ten days of this intensive combined therapy the left shoulder was noted to be swollen. Roentgenogram showed osteomyelitis with fragmentation of the cortex and periosteal elevation of the head and neck of the humerus.

Aspiration of the shoulder joint released a small amount of pus which contained a hemolytic *Staph. aureus* (Table I). For the twenty-one succeeding days, 8,000 units (10,000 units once, 15,000 units twice) of penicillin in one to 2 c.c. of saline or distilled water were injected daily into the left shoulder joint. Pus was not encountered on all occasions; when present, cultures were positive for hemolytic *Staph. aureus*, even on the twenty-first day of intra-articular therapy. Roentgenogram on the ninth day of topical therapy was interpreted as pyarthrosis with infectious chondritis and early osteomyelitis, and on the eighteenth day as pyogenic arthritis, apparently healing, with destruction of upper end of humerus. Intramuscular penicillin therapy was continued and the blood culture became sterile. Persistence of leucocytosis and fever was attributed to other active foci of infection, renal abscesses.

The extreme resistance of the organism to penicillin was confirmed by in vitro tests (survival of organism in a concentration of 6 units per cubic centimeter). A single intra-articular injection of 15,000 units of penicillin was given on Dec. 13, 1944. The following week three massive doses of 100,000 units in 2 c.c. of water were given intra-articularly at two-day intervals. No pus was obtained for culture. Intramuscular penicillin was discontinued on Dec. 16, 1944, but sulfadiazine was maintained with blood levels of 6 to 8 mg. per cent for three more months. Roentgenograms two weeks after the last intra-articular injection showed distention of the joint capsule with residual osteomyelitis (Fig. 1). No further treatment was given nor were further roentgenograms taken.

The child succumbed to chronic pyelonephritis eleven months later. Although the left shoulder remained larger than the right, there was no limitation in active or passive motion. On gross examination at autopsy, the left humerus and shoulder joint were found to be entirely normal.

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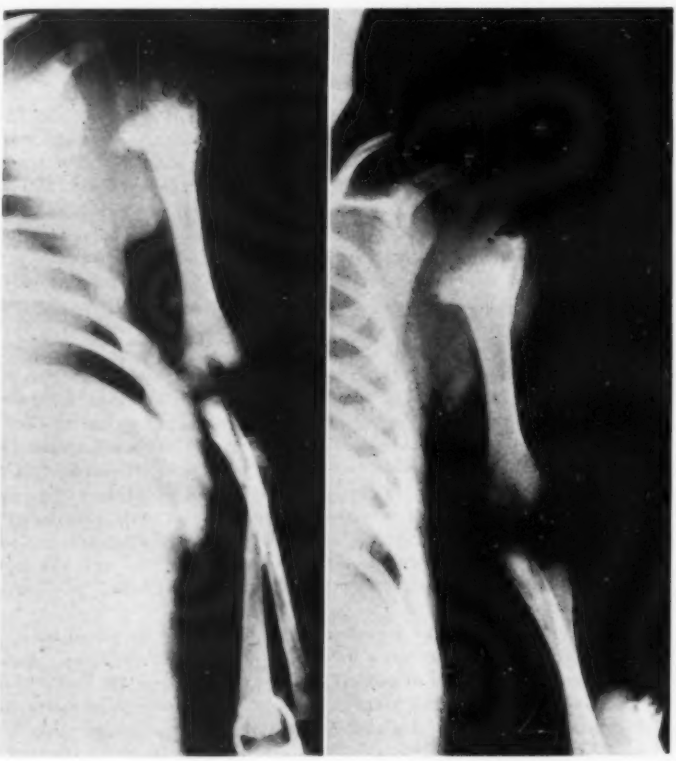
CASE 2.—J. P., a white girl of 5 months, was admitted on Feb. 13, 1945. Three weeks prior to admission the child's right arm was forcibly pulled. The next day she was irritable, had a poor appetite and resented movement of that arm. Her temperature was 38.3° C. On physical examination in the outpatient department two days later, it was noted that she favored the right shoulder, but there were no objective signs. Roentgenogram of the shoulder was negative and the total white blood cell and differential counts were normal. The function of the arm improved, but she ran a persistent, low-grade fever which rose to between 39.4° C. and 40.6° C. during the last three days at home. On the morning of admission the right shoulder became red and swollen. The child appeared acutely ill with a temperature of 38.6° C. The right arm was held in partial abduction and external rotation. There was marked swelling of the deltoid area extending into the neck; the circumference of the right shoulder (around the axilla) being 5½ cm. greater than the left. There was no increased heat or fluctuation. The remainder of the examination was negative.



*A.* *B.*

Fig. 1 (Case 1).—*A*, Roentgenogram on ninth day of topical therapy. *B*, Roentgenogram two weeks after last intra-articular injection.

The leucocyte count was 34,200 with 5 per cent lymphocytes, 1 per cent monocytes, 72 per cent mature and 22 per cent immature polymorphonuclear cells. Cultures of the nose, throat and blood showed pneumococcus type VII. Initial roentgenogram showed distention of the right shoulder joint, rarefaction of the proximal metaphyseal end of the humerus and obliteration of the smaller, proximal, epiphyseal center (Fig. 2).

*A.* *B.* *C.*

Fig. 2 (Case 2).—*A*, Roentgenogram on admission. *B*, Roentgenogram after one week. *C*, Roentgenogram one year after discharge.

TABLE

| CASES | NAME AND AGE | ORGANISM | JOINT | DURATION OF ILLNESS BEFORE ADMISSION | BLOOD CULTURE | TOTAL UNITS INTRA-ARTICULAR PENICILLIN | INTRA-ARTICULAR DOSES (NO.) | OTHER TREATMENT AND DURATION |
|---|---|---|---|---|---|---|---|---|
| 1 | M. P., 10 days | Hemolytic *Staph. aureus* | Left shoulder | 17 days | Pos. | 504,000 | 25 | Sulfadiazine throughout; penicillin I.M. until 4 days before last intra-articular injection |
| 2 | J. P., 5 mo. | Pneumococcus VII | Right shoulder | 20 days | Pos. | 500,000 | 7 | Sulfadiazine from 6 to 20th day; penicillin I.M. first 6 days |
| 3 | C. S., 3½ yr. | Beta hemolytic streptococcus | Right knee | 2 days | Neg. | 1,101,000 | 10 | Sulfadiazine 2nd to 15th day; penicillin I.M. first 11 days |
| 4 | R. H., 7 yr. | Hemolytic *Staph. aureus* | Left elbow | 3 mo. | Neg. | 765,000 | 8 | Penicillin I.M. before admission and 75 days in hospital |

The diagnosis of acute pyarthrosis of the right shoulder and osteomyelitis of the adjacent humerus was confirmed by aspiration of the joint which produced 10 c.c. of creamy pus. Smear of the exudate revealed many white cells and intracellular and extracellular gram-positive diplococci, proved on culture to be pneumococcus type VII. Sodium penicillin (100,000 units dissolved in 10 c.c. of sterile water) was injected with ease into the joint. Concomitantly, 10,000 units of penicillin were given intramuscularly every three hours.

Aspiration of the joint after thirty-six hours yielded 6 c.c. of pus containing many white cells and a few organisms. In all, penicillin was injected intra-articularly seven times over a period of nine days in doses of 50,000 to 100,000 units dissolved in 2 to 10 c.c. of water, the total dosage being 500,000 units. Intramuscular penicillin was discontinued on the sixth day, and sulfadiazine was begun and continued for the next two weeks in a daily dosage of 0.2 Gm. per kilogram of body weight per day. Blood levels ranged between 4 and 10 mg. per cent. Physiotherapy was confined to hot packs from the eleventh to the twentieth day. Small, whole blood transfusions were administered early in the course as supportive therapy.

All except the first culture of the aspirated pus were negative; no organisms were seen on smear after the fourth treatment. Eight days after the last topical injection, no fluid could be aspirated from the joint. On the sixth hospital day, motion of the shoulder became freer and less painful. Passive motion was painless in one week, and vigorous active motion returned in one month. Serial roentgenograms showed progressive improvement (Fig. 2). The temperature was normal after the first twelve hours. The white blood cell count fell to 17,000 the day after admission, remained between 15,500 and 20,000 with a shift to the left for thirteen days, after which it was normal. Nose, throat, and blood cultures were negative for pneumococcus on the tenth day. Sedimentation rate was normal on the sixteenth day.

The patient was discharged March 16, 1945. The last roentgenogram taken one year after the onset (Fig. 2) showed no abnormality in the joint and minimal thickening of

| INTERVAL BEFORE NORMAL TEMPERATURE | INTERVAL BEFORE NORMAL W.B.C. | INTERVAL BEFORE NEGATIVE JOINT CULTURE | DAYS IN HOSPITAL | FOLLOW-UP | |
|---|---|---|---|---|---|
| | | | | DURATION | CONDITION |
| Never (see history) | Never (see history) | About 28 days | 401 (see history) | Died at 13 months of chronic pyelonephritis; postmortem examination of joint was negative | |
| 12 hours | 13 days | 1 day | 30 | 1 year | General health excellent; afebrile; no local pain or deformity; no limitation of motion in joint; x-ray negative |
| 8 days | 8 days | 2 days | 30 | 9 months | General health excellent; afebrile; no local pain or limitation of motion; metaphysis broader in involved leg; x-ray shows roughening of articular surface |
| 36 days | Never elevated | 6 days | 86 | 3 months | General health excellent; afebrile; persistent wasting of musculature of arm; extension limited to 170°; still gets physical therapy; x-ray shows healing bone and normal joint |

the lateral cortex of the upper humerus. When last seen on March 22, 1946, the child was in excellent general health, and there was no pain, deformity, or limitation of motion in the right shoulder.

CASE 3.—C. S., a white girl of 3½ years, had a tonsillectomy and adenoidectomy at another hospital nine days prior to admission. Seven days later she complained of pain in the right leg and felt feverish. She was admitted on May 16, 1945, appearing acutely ill, with a temperature of 40.8° C. Impetiginous lesions were present on the face; the tonsillectomy site was healing. The right knee was hot, red, and swollen, held rigidly at a 90 degree angle, and was extremely painful on motion.

The leucocyte count was 19,000 with 74 per cent polymorphonuclear cells, 10 per cent of which were band forms. Nose and throat cultures produced a heavy growth of beta hemolytic streptococcus; blood culture was sterile. Roentgenogram demonstrated marked distention of the joint space, bulging in the popliteal fossa, and anterior displacement of the patella (Fig. 3).

The joint was aspirated, and 2 c.c. of thick, yellow-green pus was withdrawn which contained beta hemolytic streptococcus by culture; organisms and pus cells were seen on smear. Treatment consisted of daily aspirations and instillations of 100,000 units of penicillin for two days, then 100,000 units in both the medial and lateral compartments of the right knee for four days; the diluent was distilled water in amounts equal to the pus withdrawn and ranged from 2 to 8 c.c. The total intra-articular dose was 1,101,000 units. In addition, penicillin was given intramuscularly, 20,000 units every three hours for a week, then 10,000 units at three-hour intervals for five days. Two blood transfusions were given during the first forty-eight hours.

All cultures from the knee were sterile after the second day, but smears continued to show gram-positive cocci for six days. Afternoon fever of 38.6° C. persisted for eight days after admission; thereafter temperature was normal. The white blood count fell steadily and reached normal on the eighth day. For the first three days the child's gen-

eral condition was critical, but then rapid improvement ensued. Active motion of the leg was achieved on the fifth day; weight bearing was permitted on the tenth day, and after two weeks she could walk alone without pain and with only a slight limp. There was no limitation to passive motion. She was discharged on June 15, 1945, and thereafter received a course of infrared therapy and active-passive exercises.

*A.*

*B.*

Fig. 3 (Case 3).—*A*, Roentgenogram on admission. *B*, Roentgenogram nine months after discharge.

The last roentgenogram was taken on March 22, 1946 (ten months after onset), and demonstrated residual irregularity of the articular surfaces. The child has remained well without pain or limitation of motion in the right knee and runs without difficulty. The region over the medial aspect of the metaphysis of the right knee was prominent, and that leg was half an inch greater in circumference than the left.

CASE 4.—R. H., a white boy of 7 years, was in good health until July 29, 1945, when he developed a fever of 38.9° C. and severe pain and swelling of the left elbow. He was put to bed and given salicylates and local heat for one week. The fever subsided but the local pain and swelling persisted. In early August, four intramuscular injections of penicillin in beeswax were given at two-day intervals, 300,000 units per dose. The pain diminished promptly. Despite infrared radiation for one month and alternating ten-day courses of salicylates and sulfadiazine for approximately six weeks, the swelling of the elbow increased and local heat and pain recurred. On Sept. 7 and Sept. 20, 1945, the joint was aspirated; the cloudy fluid was sterile on culture and roentgenogram of the elbow was reported as negative. A cast was applied for two weeks. The patient remained in bed with an evening oral temperature of 37.8° C.

The boy was admitted to the New York Hospital on Oct. 24, 1945, eleven weeks after the onset of the illness. He was well nourished, not appearing acutely ill, with temperature of 38.5° C. There was moderate wasting of the muscle groups of the left arm and forearm. The elbow was swollen, fluctuant, slightly red, and tender about the olecranon. Motion in all planes (including pronation and supination) was limited to 10 degrees.

*A.* *B.*

Fig. 4 (Case 4).—*A*, Roentgenogram on admission. *B*, Roentgenogram two months after discharge.

Hemoglobin was 10 Gm., red cell count 4,500,000; the leucocytes were 12,200 with 41 per cent polymorphonuclear cells, of which 12 per cent were band forms. Corrected sedimentation rate was 1.45 mm. per minute (normal up to 0.4). Mantoux test and blood culture were negative. Roentgenogram of the elbow on admission showed destruction of the capitellum and trochlea, thickening of the periosteum of the humerus, and fusiform distention of the joint capsule, diagnosed as suppurative arthritis with associated osteomyelitis (Fig. 4). Five cubic centimeters of purulent fluid were aspirated from the involved joint; no organism was observed on smear, but hemolytic *Staph. aureus* was cultured. It was later found to be sensitive to 0.082 units of penicillin per cubic centimeter in vitro.

In the first two weeks the patient was given 10,000 units of penicillin sodium intramuscularly every three hours. Seven joint aspirations were performed, each with replacement by

100,000 units of penicillin in distilled water. Ten days after the last dose of this intensive regimen, aspiration yielded no pus, and 65,000 units were injected, making a total intra-articular dosage of 765,000 units. Intramuscular penicillin was continued for eleven weeks for a total of 8,132,000 units. After the first two aspirations, all cultures and smears were negative. Roentgenographic evidence of improvement was slow. The total white count was normal, but there was persistent elevation of band forms. Sedimentation rate reached a normal level after seventy days. Low-grade fever disappeared after thirty-six days. The arm was never immobilized, and active motion was encouraged. Physical therapy (whirlpool and active-passive exercise) was instituted after the fiftieth day. The return in the range of motion is tabulated in Table II. The boy was discharged on Jan. 18, 1946, after twelve weeks of hospitalization, physical therapy being continued.

TABLE II. IMPROVEMENT IN RANGE OF MOTION FOLLOWING INTRA-ARTICULAR PENICILLIN THERAPY

| DATE | DAYS | FLEXION-EXTENSION | PRONATION-SUPINATION |
|---|---|---|---|
| 10/24/45 | Admission | 10 degrees | 10 degrees |
| 11/15/45 | 22 | 45 degrees | 80 degrees |
| 1/ 7/46 | 75 | 80 degrees | 80 degrees |
| 1/17/46 | 85 (Discharge) | 140 degrees | 90 degrees |
| 3/26/46 | 153 | 170 degrees | 90 degrees |

The last roentgenogram on April 11, 1946, demonstrated that the capitellum and trochlea were beginning to reform and there was no distention of the joint capsule (Fig. 4). Periosteal proliferation was decreased and general appearance of bone structure improved. There was no evidence of active destructive process. At this time the boy seemed in excellent health and had no complaints. There was still some wasting of the muscle groups of the left arm which exaggerated the bony prominences about the elbow. Extension of the arm could not be performed beyond 170 degrees, but he used that extremity without pain or awkwardness. No other movements were limited.

## DISCUSSION

*Organism.*—The infecting organisms were all gram-positive: hemolytic *Staph. aureus* in two cases; beta hemolytic streptococcus in one; pneumococcus type VII in one. Blood cultures were positive in two cases. As in the experience with other penicillin-treated infections, hemolytic *Staph. aureus* was the most difficult to manage. The strain in Case 1 was resistant in vitro to penicillin concentrations of 6 units per cubic centimeter.

*Source of Infection.*—In one case (Case 4) no antecedent cause could be identified; whether the pyarthrosis was primary or secondary to osteomyelitis could not be determined. The newborn infant (Case 1) may have developed bacteriemia from an infected cut-down site. Osteomyelitis probably preceded the joint infection here and in Case 2, where local trauma initiated the disease. The other case (Case 3) was an uncomplicated pyarthrosis, the blood stream presumably having been invaded from open wounds in the throat or on the face.

*Treatment.*—Intra-articular injections of penicillin in large dosage were continued for as long as pus could be aspirated from the joint, even if previous cultures were negative. When the pus was sterile on culture it was interpreted as being due to the presence of penicillin in the exudate and the resultant inhibition of growth on culture media.

The hazard of undertreatment should be emphasized. Sterilization of the joint was not achieved in the infant (Case 1) with twenty-one daily intra-articular injections of 8,000 units each. The extreme resistance of the organism which was then discovered justified the massive dose (100,000 units) used thereafter. The small amount of diluent (2 c.c.) was determined by the limited amount of pus withdrawn on aspiration. Treatment was discontinued arbitrarily after three such doses with no recurrence. Dosage of this magnitude and in these high concentrations did not increase local discomfort; similar intensive topical therapy has been reported.[7] In Case 4, inadequate therapy at home served only to ameliorate the symptoms and to send the disease into a chronic course. The large total dosage in Case 3 was due to the presence of two noncommunicating pus pockets in the knee, each being treated separately.

Intramuscular penicillin was administered because of the gravity of the disease, the presence of positive blood cultures in two cases, and of osteomyelitis in three cases. Whether systemic therapy is necessary in all cases of pyarthrosis is not definitely determined.

Rammelkamp and Keefer[8] demonstrated penicillin in the blood stream after intra-articular injection, and Bagley[7] has proposed this site as the preferred one for parenteral injection, even in the absence of joint disease. By use of massive dosage he showed that therapeutic blood levels can be achieved. On theoretical grounds, intra-articular penicillin should sterilize the joint directly and the blood stream and other foci of infection secondarily. This remains to be proved clinically. On the other hand, it has been demonstrated by Tillett and associates[9] that intravenous penicillin can sterilize a pneumococcal infection of the joint; and Balboni and associates[10] found that intramuscular penicillin penetrates the joint in a high concentration, disappears slowly, and does not accumulate. These results might imply that aspiration and intra-articular therapy are not necessary. Nevertheless, it would seem preferable to evacuate the pus by aspiration in the presence of pyarthrosis and to allay concomitant discomfort rather than to await spontaneous resorption. The optimal route of administration and dosage is still to be determined.

In three cases oral sulfadiazine was given. The first infant (Case 1) was desperately ill, and all available therapeutic agents seemed indicated. However, the pyarthrosis developed after a three-week course of sulfadiazine. In Case 3, the child remained critically ill after twenty-four hours of penicillin therapy, hence sulfadiazine was added to the therapeutic armamentarium. Sulfadiazine was given late in Case 2 after marked clinical improvement on penicillin alone. We have no definite evidence that sulfadiazine shortened the course of the pyarthrosis in these cases.

The question of the advisability of surgical intervention was raised in Cases 3 and 4 because of the failure of immediate response and the development of separate pus pockets within the same joint in the former and the chronicity of the disease and adjacent osteomyelitis in the latter. A recent paper[11] recommends early surgery as a means of facilitating local instillation of penicillin when pyarthrosis complicates staphylococcal osteomyelitis. However, open drainage increases the likelihood of subsequent limitation of motion

in the joint. Therefore, we preferred to allow a therapeutic trial of intramuscular and intra-articular penicillin first, and were gratified with the outcome both in curing the patients and in restoring full function to the involved joints.

*Course.*—The hospital course was remarkably brief and uneventful, considering the nature of the disease, except in the first patient, who had other complications. In the other three cases, within a week after the first intra-articular dose the children had regained partial use of the affected joint and seemed well on the way to recovery. They were spared immobilization in cumbersome dressings and casts, and the only trauma was from the aspirations. Their general improvement in health was gratifying.

## SUMMARY

Four cases of suppurative arthritis in infants and children have been presented, in which surgical intervention was not required. Three were in the acute stage of the disease and one in the chronic stage, and adjacent osteomyelitis was present in three. All were treated by joint aspiration and intra-articular instillation of penicillin. Supplemental therapy consisted of intramuscular penicillin in all, oral sulfadiazine in three, transfusions, and physiotherapy.

Three surviving patients were seen after discharge at three, nine, and twelve months, respectively, with complete return of function in the last two and without recurrence in any.

It is suggested on a theoretical basis that intra-articular penicillin therapy alone in large dosage may be adequate.

Acknowledgment is made to Dr. H. Temple and Dr. A. J. Tillinghast of the Department of Roentgenology of the New York Hospital for reviewing the films.

## REFERENCES

1. Keefer, C. S., and others: J. A. M. A. **122**: 1217, 1943.
2. Ravdin, I. S., and Johnston, C. G.: Am. J. M. Sc. **208**: 248, 1944.
3. Dawson, M. H., and Hobby, G. L.: J. A. M. A. **124**: 611, 1944.
4. Herrell, W. E., Nichols, D. R., and Heilman, D. H.: J. A. M. A. **125**: 1003, 1944.
5. Anderson, D. G.: New England J. Med. **232**: 400, 1945.
6. Herrell, W. E., and Kennedy, L. J.: J. PEDIAT. **25**: 505, 1944.
7. Bagley, W. R.: South. Med. & Surg. **107**: 180, 1945.
8. Rammelkamp, C. H., and Keefer, C. S.: J. Clin. Investigation **22**: 425, 1943.
9. Tillett, W. S., McCormack, J. E., and Cambier, M. J.: J. Clin. Investigation **24**: 595, 1945.
10. Balboni, V. G., Shapiro, L. M., and Kydd, D. M.: Am. J. M. Sc. **210**: 588, 1945.
11. Anderson, D. G.: New England J. Med. **232**: 423, 1945.

# THE DYNAMICS OF NEWLY BORN BABIES

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THE present paper attempts to lend a hand in the spade work of fact-finding about infantile responses. The term "dynamics" as used in this paper was first employed by Dr. C. Anderson Aldrich, who observed in young infants a specific reaction to an applied force. The muscular energy which the baby releases to resist such force is called "dynamics."

Extensive studies have been carried out in an effort to establish some fundamental facts concerning the dynamics of newly born babies. Two major lines of investigation were followed. First, how do young infants respond to a specific force, in this case a pull on the arms and legs? Second, to what extent is this response influenced by the physical make-up of the child and a variety of factors concerning his delivery?

This study gives an answer to these basic questions only. The wider implications of knowledge of the baby's dynamics can as yet only be surmised. There may be a correlation between what is called dynamics and the inherent emotional qualities of the baby. To shed light on this and establish the meaning of the dynamics of the newly born infant will be the task of further investigation. Follow-up observations are being made on the development of all of the children examined in the present study.

## METHOD

The observations were made in the nursery for newly born infants of the maternity ward at St. Mary's Hospital, Rochester, Minn. Altogether, the dynamics of 689 babies, delivered between February and November, 1944, were determined. Each infant was graded twice. The first test was carried out within twenty-four hours after birth and the second, eight days after delivery. In those cases in which the two tests produced different results the mean figure was established.

Factors which might influence the infant's reactions were examined and statistically evaluated. For the baby these consisted of sex, weight, and pathologic findings. For the mother they included the type of delivery, length of labor, sedation administered during labor, and serious illnesses.

The actual test was simple. The baby was placed on his back on an examining table with his legs apart and his buttocks braced against a small upholstered support. The examiner then held the infant by his hands and forearms and gently lifted him up into a sitting position. Next, the infant was returned to his supine posture and the examiner attempted to straighten his legs with a

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From the Rochester Child Health Project.

slow pull. The child's response was classified according to his resistance to the test. Two extremes were found. At one extreme (Fig. 1) the child did not resist and his body was limp: (1) the head fell back, pulled down by its own weight, (2) the arms were straightened without noticeable resistance from the baby, and (3) the legs followed easily the pull of the examining hand. At the other extreme (Fig. 2) the child resisted and his body showed strong muscular tension: (1) the head was actively lifted up and held, (2) the biceps contracted and the elbow joints formed a sharp angle, (3) the pull on the legs produced an intense contraction at the knee and hip joints.

Fig. 1.—Grade 1 of dynamics.

A scale from 1 to 4 has been adopted for the varying degrees of the babies' resistance. Complete yielding limpness constitutes grade 1 of dynamics. Strong muscular resistance represents grade 4. Grades 2 and 3 accordingly stand for the two intermediate degrees.

## RESULTS

*Grade Distribution of Total Number of Children.*—When tested for their dynamics, the 689 babies showed a remarkable preponderance of grades 2 and 3 as shown in Table I. The two extremes, grades 1 and 4, represented only 4.6

per cent of the total. At the same time the general tendency was clearly toward the lower rather than toward the higher grades. Most outstanding of all was the small number of infants given top marks with only six infants placed in grade 4.

*Sex in Relation to Dynamics.*—Together, the two middle grades show very little variation as between the two sexes, accounting as they do for 95.8 per cent of the boys and 94.8 per cent of the girls. A somewhat different picture becomes apparent if the two lower "passive" grades are compared with the two higher "active" grades. It then appears that 31.8 per cent of the boys are placed in grades 3 and 4 as against 25.0 per cent of the girls. A more obvious discrepancy between the sexes is seen in grade 4 with its one girl and five boys.

TABLE I. THE DISTRIBUTION OF DYNAMICS ACCORDING TO SEX

| DYNAMICS, GRADE | TOTAL | | BOYS | | GIRLS | |
|---|---|---|---|---|---|---|
| | NUMBER | PER CENT* | NUMBER | PER CENT* | NUMBER | PER CENT* |
| 1 | 26 | 4 | 11 | 3 | 15 | 5 |
| 2 | 465 | 67 | 249 | 65 | 216 | 70 |
| 3 | 192 | 28 | 116 | 31 | 76 | 25 |
| 4 | 6 | 1 | 5 | 1 | 1 | 0.3 |
| Total | 689 | 100 | 381 | 100 | 308 | 100 |

*Percentages based on totals in group.

*Weight in Relation to Dynamics.*—The average weight in grams of the babies in each group was calculated and compared. The weight of the infants in grade 1 averaged 3,183 Gm. The respective figures for grades 2, 3 and 4 were: 3,521 Gm., 3,437 Gm., and 3,583 Gm. The average weight of grades 1 and 2 was 3,503 Gm. and that of grades 3 and 4 was 3,441 Gm.

*Pathologic Findings in Babies and Mothers in Relation to Dynamics.*—The fact that the response of the infants to outside stimuli might have been influenced by their physical status at the time of the test had to be considered. Attention was paid, however, only to illnesses serious enough to interfere with the child's normal activity at that age. All heart murmurs were noted, since an organic heart lesion could not always be excluded. Brain injury (diagnosed by fairly definite symptoms such as one-sided convulsions), Mongolian idiocy, dystrophies, and respiratory difficulties were regarded as possible causes which might interfere with the baby's normal reaction to the applied force of the test.

Examination of Table II shows a clearly marked trend from grade 1 to grade 3. The relative incidence of pathologic findings is highest in grade 1, with 23 per cent in a group of twenty-six. It declines sharply to 4 per cent in grade

TABLE II. DYNAMICS VERSUS BABY'S PATHOLOGIC CONDITION

| DYNAMICS, GRADE | TOTAL BABIES | CHILDREN WITH ABNORMALITIES OR THAT DIED | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | TOTAL | PER CENT* | HEART MURMUR | CENTRAL NERVOUS SYSTEM | MONGOLIAN IDIOT† | ATELECTASIS | RESPIRATORY DIFFICULTY | DIED |
| 1 | 26 | 6 | 23 | | 1 | **2** | **1** | | 2 |
| 2 | 465 | 18 | 4 | 12 | 4 | **1** | | **1** | |
| 3 | 192 | 5 | 3 | 2 | 3 | | | | |
| 4 | 6 | 1 | 17 | 1 | | | | | |
| Total | 689 | 30 | 4 | 15 | 8 | 3 | 1 | 1 | 2 |

*Percentage based on total number of children who had the grade of dynamics.
†And dystrophy.

2, and 3 per cent in grade 3. Then follows a sudden rise to 17 per cent in grade 4, a rise which, however, is scarcely conclusive, owing to the smallness of the group in this grade. There are only six infants in grade 4 and one of them was found to have a heart murmur. To remove the factor of the small number in the extreme grades, grades 1 and 2 have been added and have been compared with grades 3 and 4. The result is 5 and 3 per cent respectively. In other words, the prevalence of pathologic findings is nearly twice as high in the lower grades as in the higher grades.

Fig. 2.—Grade 4 of dynamics.

It was further considered that certain pathologic conditions in the mother at the time of delivery might have had a temporary influence on the behavior of the child (Table III). Toxemia, diabetes, and syphilis in the mother were tabulated for this reason. Here again, as in the infants, the incidence of illness is highest in the lower grades. Ten per cent of the mothers of infants in grades 1 and 2 had pathologic conditions as compared with 5 per cent among those of grades 3 and 4.

TABLE III. DYNAMICS IN RELATION TO VARIOUS PATHOLOGIC CONDITIONS OF MOTHERS

| DYNAMICS, GRADE | TOTAL CHILDREN | MOTHERS WITH VARIOUS PATHOLOGIC CONDITIONS | | | | |
|---|---|---|---|---|---|---|
| | | TOTAL | PER CENT* | TOXEMIA | DIABETES | SYPHILIS |
| 1 | 26 | 4 | 15 | 2 | 2 | |
| 2 | 465 | 43 | 9 | 41 | 1 | 1 |
| 3 | 192 | 9 | 5 | 8 | | 1 |
| 4 | 6 | | | | | |
| Total | 689 | 56† | 8 | 51 | 3 | 2 |

*Percentages based on number of children in the group with the particular grade of dynamics.

†Actually fifty-four mothers with pathologic conditions because two of them had more than one pathologic condition.

*Method of Delivery in Relation to Dynamics.*—Since complications during delivery and length of labor might have a transitory or lasting effect on the dynamics of the infant, both these factors were included in the investigation. A distinction was drawn between cesarean section, delivery by forceps, and spontaneous birth. Breech deliveries were classed separately in view of the fact that the breech position of the baby often adds to the difficulties of the birth.

As shown in Table IV, the proportion of spontaneous births to the total of deliveries varies but little and shows no clear trend if each group is considered singly. The number of spontaneous births is eighteen births or 69 per cent of all the births in grade 1, rises to 338 or 72.7 per cent in grade 2 and 147 or 76.6 per cent in grade 3, only to fall again to four births or 67 per cent in grade 4. If grades 1 and 2 are compared with grades 3 and 4, it appears that in the two lower grades the spontaneous births account for 73 per cent of the total deliveries in those grades whereas in the two higher groups this figure stands slightly higher at 76 per cent.

Of twenty-three babies who had breech presentation, three were classed in grade 1 and none in grade 4. On the other hand, a comparison between grades 1 and 2, with their seventeen breech deliveries, and grades 3 and 4, with six, shows that the proportion of breech deliveries in relation to the total number of infants is approximately the same in the two major groups.

Calculations of the length of labor showed the following average figures for each grade: for babies in grade 1 the average length of labor was 489 minutes; for grade 2, 619 minutes; for grade 3, 537 minutes and for grade 4, 555 minutes.

*Sedation Administered During Labor in Relation to Dynamics.*—By far the most important sedatives administered to mothers during labor were pentobarbital sodium (nembutal) and demerol, either combined or separately. Colonic ether was used mainly in conjunction with pentobarbital sodium or demerol or both, while seconal was of very little importance. In ninety-one cases no analgesic agent was administered.

Pentobarbital sodium and demerol combined were employed as sedatives for 248 mothers. As shown in Table V, a higher degree of sedation is recorded in this group for the mothers of babies whose dynamics were graded 3 and 4 than for mothers of babies whose dynamics were of the two lower grades. Exactly the opposite picture is shown by the record of the administration to 223 mothers of pentobarbital sodium alone. Here the average dose was highest for mothers of infants whose dynamics were graded 1 and 2.

For the two most important analgesic agents, therefore, no clear relation was noted between the average doses given to the mother and the dynamics of the infant. The same is true for the other sedatives administered either singly or in various combinations.

*Changes in Dynamics From the First to the Second Examination.*—The first examination of the infant was carried out within twenty-four hours after birth. In order to establish the immutability or inimmutability of the results obtained, a second examination was made eight days after delivery. The examiner did not know the result of the first test at the time of the second.

TABLE IV. THE PERCENTAGE DISTRIBUTION OF DYNAMICS ACCORDING TO METHOD OF DELIVERY

| DYNAMICS, GRADE | TOTAL CHILDREN | METHOD OF DELIVERY | | | BREECH PRESENTATION (PER CENT†) | |
|---|---|---|---|---|---|---|
| | | CESAREAN A PER CENT* | FORCEPS B PER CENT* | SPONTANEOUS C PER CENT* | FORCEPS | SPONTANEOUS |
| 1 | 26 | | 31 | 69 | 4 | 8 |
| 2 | 465 | 2 | 25 | 73 | 1 | 2 |
| 3 | 192 | 2 | 22 | 77 | 1 | 2 |
| 4 | 6 | | 33 | 67 | | |
| Total | 689 | 2 | 25 | 74 | 1 | 2 |

*Percentages based on total number of children who had the grade of dynamics.
†Included in columns B and C.

TABLE V. SEDATION DURING LABOR CONSIDERED IN RELATION TO DYNAMICS

| DYNAMICS, GRADE | PENTOBARBITAL SODIUM | | PENTOBARBITAL SODIUM AND DEMEROL | | | PENTOBARBITAL SODIUM, DEMEROL, AND COLONIC ETHER | | | | PENTOBARBITAL SODIUM AND ETHER | | | OTHER SEDATION (NO. CASES) | NO SEDATION (NO. CASES) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NO. CASES | GRAINS* | NO. CASES | PENTOBARBITAL SODIUM (GRAINS)* | DEMEROL (MG.)* | NO. CASES | PENTOBARBITAL SODIUM (GRAINS)* | DEMEROL (MG.)* | ETHER (OUNCES)* | NO. CASES | PENTOBARBITAL SODIUM (GRAINS)* | ETHER (OUNCES)* | | |
| 1 | 13 | 3.7 | 7 | 3.9 | 135.7 | | | | | 1 | 4.5 | 1.5 | 1 | 4 |
| 2 | 150 | 3.5 | 172 | 3.8 | 109.6 | 34 | 4.4 | 138.2 | 2.9 | 29 | 3.8 | 3.2 | 21 | 59 |
| 3 | 58 | 3.2 | 67 | 3.9 | 127.6 | 18 | 4.3 | 191.2 | 2.9 | 11 | 4.4 | 2.5 | 11 | 27 |
| 4 | 2 | 3.0 | 2 | 3.0 | 150.0 | | | | | | | | 1 | 1 |
| Total | 223 | 3.4 | 248 | 3.8 | 115.5 | 52 | 4.4 | 156.5 | 2.9 | 41 | 4.0 | 3.0 | 34 | 91 |

*Average doses.

The grade of dynamics of eighty-seven newborn babies changed somewhat, but the grade of only two of these was altered by more than one point. It should be borne in mind that a very small difference in the behavior of the infant might produce a transfer from one grade to another. On the first test, for instance, the dynamics of a baby might have been classed as being between grades 1 and 2. Having to decide in which of the two grades to place the infant the examiner gave preference to grade 1. On the second test the dynamics of the child might still have been classed between the two grades, but grade 2 chosen.

Relatively, the largest number of changes are recorded in the lowest grade, with fifteen transfers from grade 1 to 2, four from 2 to 1 and two transfers from grade 1 to grade 3. For the two middle grades the changes, though numerically higher, were relatively less frequent, that is, approximately 10 per cent of the total infants in the groups 2 and 3. There were thirty-eight transfers from grade 2 to 3 and twenty-seven from 3 to 2. Only one baby was transferred from grade 3 to 4. A downward trend from the higher grades to the lower is noticeable if the transfers from grades 1 and 2 on the one hand and from grades 3 and 4 on the other are compared. The changes from the two bottom groups to the higher ones amounted to 8 per cent of their original total while in the opposite direction they represented nearly 14 per cent of the infants originally classed in the top grades.

## COMMENT

The careful observer in a nursery of newborn babies will readily notice a difference in the characteristics of the infants. Aside from their actual physical appearance, the degree of alertness, activity, amount of crying, and interest in nursing vary. The question arises as to whether or not the intensity of such expressions is dependent on an underlying make-up of the emotional constitution of the babies. In the search for a simple measure of the force which may determine the degree with which the baby responds, a reaction specific for each infant was noticed. It is felt that this reaction is an expression of the energy, the dynamics, called forth by the application of outside force. These impressions are not established facts but guides to further study, which in time may permit of more definite conclusions.

Meanwhile, we have had to content ourselves with recording basic observations. They comprised, first, the reaction of the child to the force applied, and, second, the existence of possible influences on such a reaction.

The distribution of the infants in grades of dynamics according to their reaction to the applied force might possibly foreshadow the pattern of adult emotional behavior, in that people who have outspokenly active or passive emotional qualities are fewer in number than those between the two extremes. The statistical result of this initial test, while not conclusive, encourages the hope that a method may have been found to measure the emotional expression of infants.

Perhaps the most relevant finding of our study is the minimal change of dynamics from the first to the second examination. It was determined to be 13 per cent of 689 children. This seems high, if dynamics are thought of as a persistent quality inherent in the infant. But it does not seem high when one con-

siders the influence of environmental factors and the subjectivity of the test. The fact that the dynamic reaction, determined at different times and even by different examiners, remained essentially unaltered, supports the impression that a persistently inherent quality underlies such reactions during the neonatal period.

## SUMMARY

A study of the dynamics of newly born infants has been made. Six hundred and eighty-nine infants have been examined twice during their eight-day stay in the hospital. Factors which might have influenced their dynamics have been evaluated.

Of 689 infants examined, twenty-six were classified as grade 1 (least active), 465 as grade 2, 192 as grade 3, and six as grade 4 (most active).

The sex distribution showed a prevalence of the boys in the higher grades.

No definite correlation could be established between the babies' weights and their dynamics.

A distinctive influence of pathologic findings in mother and child on the infants' dynamics was observed. The accumulation of serious defects in grade 1 and the absence of serious illnesses in grade 4 are noteworthy.

The relation of the mothers' labor and method of delivery to the grading of dynamics was inconclusive.

The investigations on the decrease and increase of dynamics from the first to the second examination showed a 13 per cent change from one grade to the next one. Two babies made a change of two grades.

The evaluation of the data obtained encourages the hope that dynamics as defined here is an inherent quality and is not decisively altered by outside factors.

# SOME EFFECTS OF INJECTED CYTOCHROME C IN MYOCARDIAL AND CEREBRAL ANOXIA IN MAN

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ANOXIA is a problem of widespread clinical interest and has been attacked from many points of view. We have been interested in the possibility of combating the effects of tissue anoxia by enhancing the tissue uptake of oxygen. In this connection we have concerned ourselves more particularly with succinic acid[1, 2] and cytochrome C.[3-8] This report deals with some effects on the heart and brain of the parenteral administration of cytochrome C under conditions of anoxia.

The method used for preparing the cytochrome C was that of Keilin and Hartree.[9] The material obtained by this method was reconcentrated by being put through the 50 per cent ammonium sulfate precipitation a second time. The material was then sterilized by passing it through a Seitz filter. The cytochrome C thus obtained seems to be nontoxic except that on two occasions it has produced a transient urticaria when injected into patients, one of whom had a history of asthma and the other, hay fever. We have found that cytochrome C appears not only to be nontoxic but that it is relatively stable in the body when injected.[7]

Cytochrome C apparently exists in organs in suboptimal amounts. That is to say, there seems to be relatively more cytochrome oxidase present in the organs than is required for activation by the cytochrome C present. Hence, an added supply of cytochrome C could be expected to be effective. We have demonstrated that it is possible in animals to increase significantly the organ content of cytochrome C.[7] The increase in organ content which we could produce following intravenous or intramuscular injection was of a magnitude sufficient to produce an in vitro increase in tissue oxygen consumption of 50 to 100 per cent. Hence, we had reason to believe that we might be able to increase the tissue uptake of oxygen in the organs of human beings by the parenteral injection of cytochrome C.

Under normal conditions there would appear to be no purpose in increasing the tissue uptake of oxygen. Under conditions of anoxia, however, such an effect would be highly desirable.

## MYOCARDIAL ANOXIA

A comparatively simple method of studying myocardial anoxia is by means of the electrocardiogram. Anoxic effects on the heart muscle are often reflected in characteristic changes in the electrocardiogram. We therefore selected

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MRS. M. F.

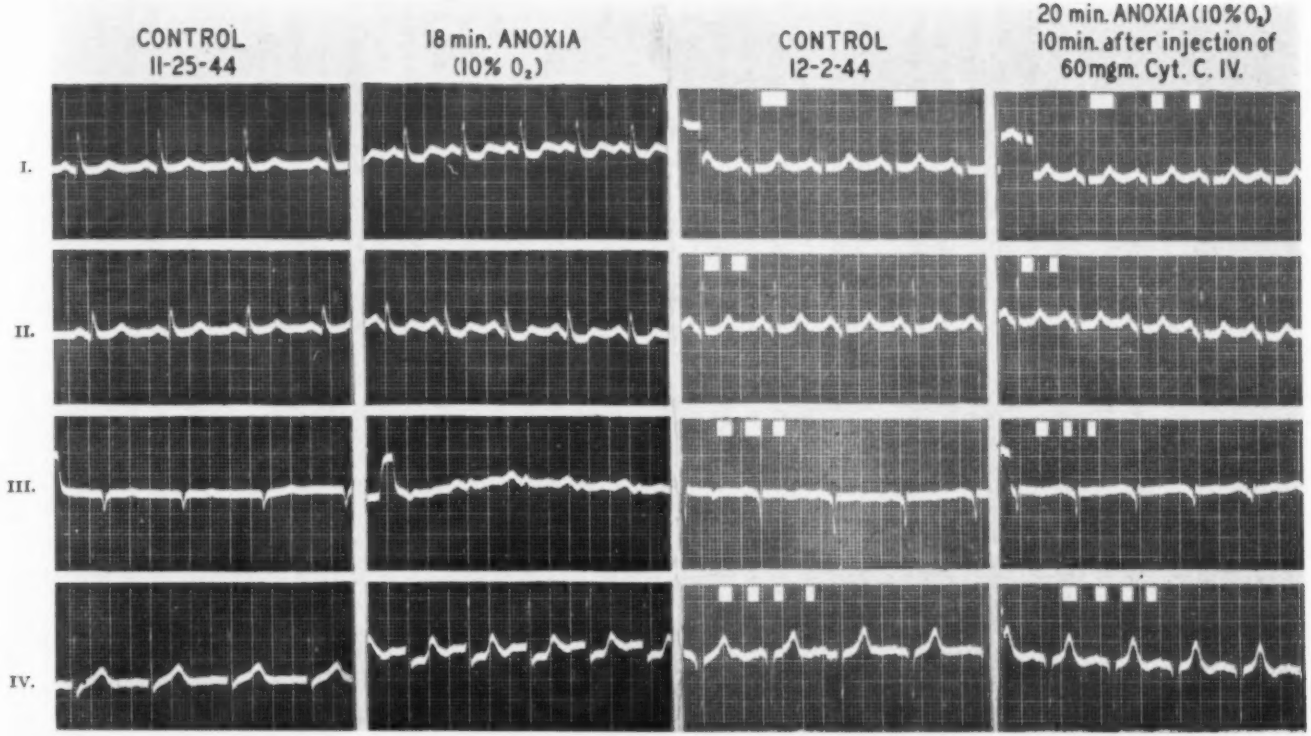


Fig. 1.—Effect of cytochrome C in preventing anoxic changes in electrocardiogram. Tracings on left show changes produced by anoxia without cytochrome C. Tracings on right show comparative lack of such changes when cytochrome C had been injected previously.

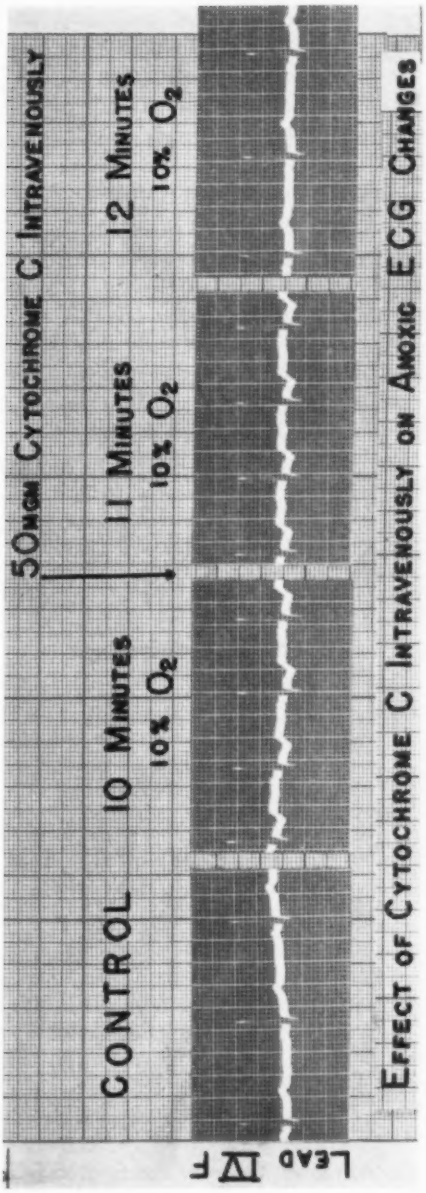
LEAD IV F
CONTROL 10 MINUTES 10% $O_2$
50 MGM CYTOCHROME C INTRAVENOUSLY
11 MINUTES 10% $O_2$
12 MINUTES 10% $O_2$
EFFECT OF CYTOCHROME C INTRAVENOUSLY ON ANOXIC ECG CHANGES

Fig. 2.

four patients who showed striking changes in the electrocardiogram following ten to twenty minutes of exposure to an atmosphere containing 10 per cent oxygen and 90 per cent nitrogen. In these four cases, as indicated by a typical response in the accompanying chart (Fig. 1), the anoxic effects could be prevented by the previous intravenous administration of 60 mg. of cytochrome C. The injected cytochrome C exerts its effect within two minutes, as may be seen in Fig. 2.

In one of the patients in whom the effects of anoxia on the electrocardiogram were studied, the anoxia could not be continued for the full twenty minutes because the patient experienced considerable subjective distress which we took to be cerebral in origin. However, even in this shorter period there were pronounced electrocardiographic changes. When the test was repeated on another day under the same conditions of anoxia, this time after the injection of 50 mg. of cytochrome C intravenously, the anoxia produced no effect on the electrocardiogram; and, what is also important, the subjective disturbances of the anoxia were eliminated and the patient was able easily to continue under the conditions of anoxia for the full twenty minutes. This sequence of events was observed in other patients whether or not there were electrocardiographic changes. That is to say, patients seemed to tolerate the anoxia much more easily if they had previously been injected with cytochrome C than if they had not had the substance. This suggested that the cytochrome C was effective in combating the effects of anoxia on the brain as well as on the heart.

### CEREBRAL ANOXIA

The measurable effects of cytochrome C on cerebral anoxia were studied through inducing anoxic effects on visual discrimination, and code transliteration. These experiments were done with the very kind cooperation of Drs. W. H. Forbes and J. I. Niven of the Harvard Fatigue Laboratory.

*Effect of Cytochrome C on Visual Discrimination.*—One of the functions which under conditions of anoxia becomes measurably impaired earliest is that of visual discrimination.[10] Two trained subjects were studied, using the Crozier and Holway discriminometer.[11] The results were almost identical in each case and are illustrated in one case in Fig. 3. It will be noted that the cytochrome C succeeds in overcoming completely the anoxic effects. In this figure the differential threshold is plotted against the time at which it was obtained. The subject looked into a binocular microscope head at a dimly illuminated circular field whose intensity was $\text{Log}_{10}$ 2.360, in milliphotons. After adaptation he was asked to report when he could distinguish a test flash of approximately $\frac{1}{10}$ of a second superimposed upon the field. $\text{Log}_{10}$ thus represents the least added intensity in milliphotons at which the subject was able to distinguish the flash. Each point on the chart represents the mean of ten observations. A rise in the threshold represents a deterioration in differential brightness sensitivity and therefore in related visual functions such as acuity. The efficacy of the cytochrome C is indicated by the fact that despite the continuing anoxia, there is a return of the threshold to its normal level as determined in room air.

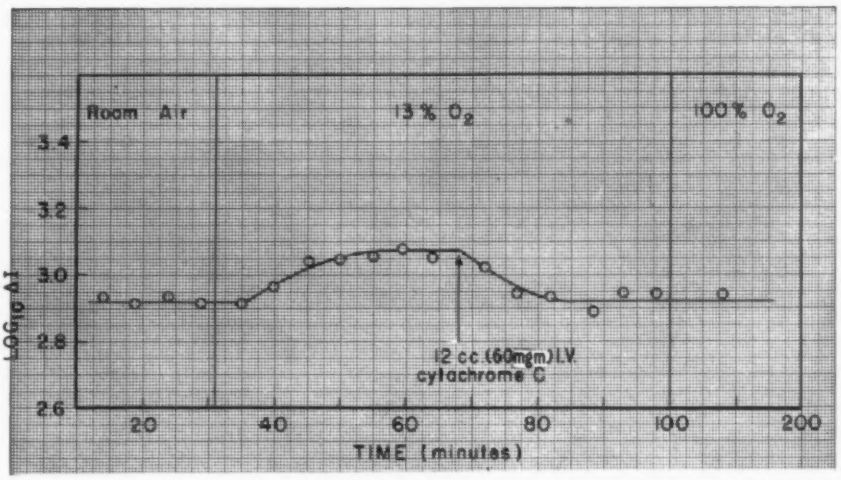


Fig. 3.—Effect of cytochrome C on visual discrimination as shown by chart of reactions of one subject tested.

*Effect of Cytochrome C on Code Transliteration.*—Johnson and Paschal[12] devised a code test which involved the maintenance of visual function, attention, memory, and neuromuscular coordination during a longer period than could be included in an ordinary voluntary spurt. The test has proved of value in measuring the effects of moderate degrees of anoxia. In the test a series of fifty letters to be transliterated must be located in the alphabet and the corresponding letter substituted. On repeated tests, different forms are used so that there is no opportunity for learning. The codes were compiled with a view to insuring the closest practicable approximation to equality of difficulty.

The studies of the effect of anoxia and cytochrome C on code transliteration were carried out in a pressure chamber. The subjects had been fasting for at least twelve hours. The time required for the code transliteration was measured first at sea level, then at a simulated altitude of 16,500 feet before and after the injection of cytochrome, and finally at sea level again. The temperature in the pressure chamber varied between 0° F. to 10° F. so that the subjects required the use of electrically heated suits.

The first experiment was carried out on four subjects. Only two of these subjects showed a definite slowing of time required for the code transliteration at the simulated altitude of 16,500 feet. Hence, it was only these two subjects on whom cytochrome C could exert a correcting beneficial effect. That it did exert such an effect can be seen in Fig. 4. In this chart each point represents the average time of four tests, each test requiring the transliteration of fifty letters into corresponding codes.

On a subsequent occasion the experiment was repeated in these two subjects, but instead of cytochrome C, 5 c.c. of normal saline in one subject and 5 c.c. of 50 per cent glucose in the other were injected intravenously. In these

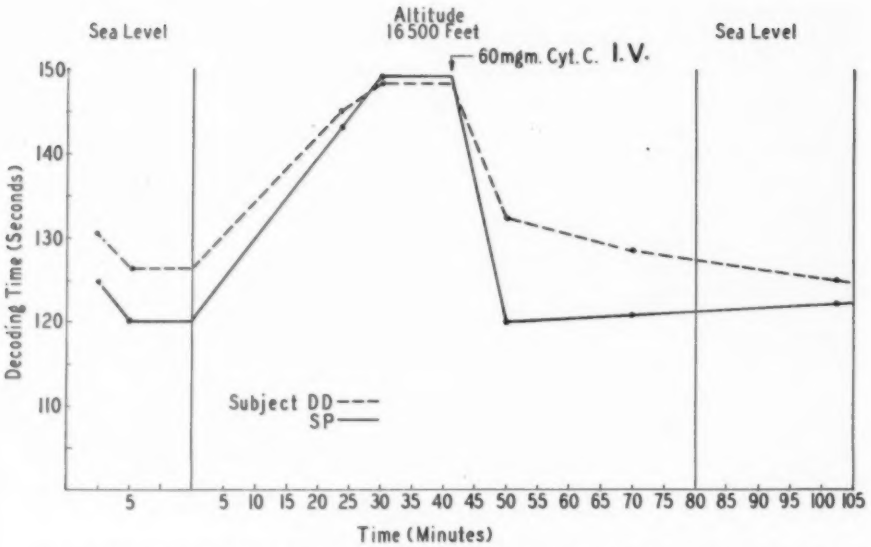


Fig. 4.—Effect of cytochrome C in code transliteration. Each point represents the average time of four tests made on the subjects, each test requiring transliterating fifty letters into corresponding codes.

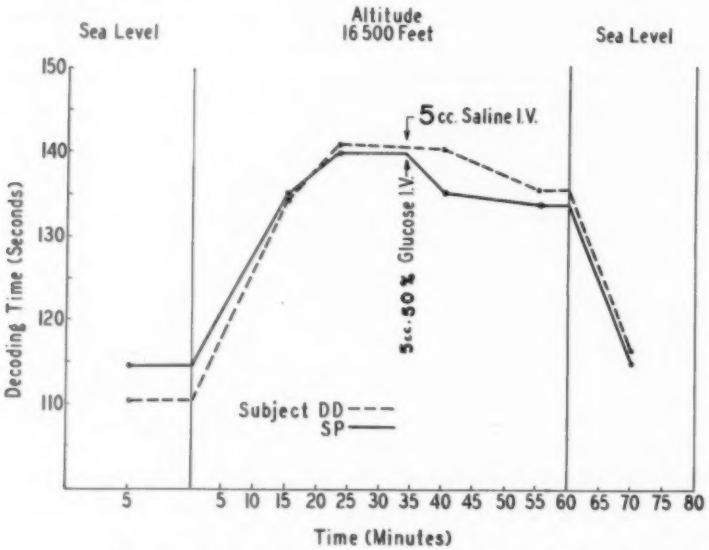


Fig. 5.—Effect of normal saline and 50 per cent glucose on the same subjects tested in Fig. 4.

observations, which served as a control, the saline and glucose had no appreciable effect as can be seen in Fig. 5, although the latter theoretically might have been expected to be somewhat beneficial.

The subjective effects of cytochrome C under conditions of anoxia are worthy of comment. We have indicated previously that following injected cytochrome C, subjects are enabled to tolerate degrees of anoxia which they could not tolerate without the injection. In the experiments in the pressure chamber, this fact was again demonstrated. The general discomfort, mental cloudiness, and torpor induced by the anoxia vanished like a clearing fog within a minute or two after the injection of the cytochrome C. As described by one subject, the sensation was as though a blurred picture were suddenly put into focus. The effect was noted despite the fact that the subjects neither knew what was being injected nor how soon it would be effective.

## DISCUSSION

Our findings suggest that cytochrome C might be beneficial in clinical conditions associated with myocardial anoxia such as angina pectoris and acute coronary occlusion. The observations which we have made on four patients with angina pectoris through the cooperation of Dr. J. E. F. Riseman indicate that cytochrome C is only moderately effective in increasing the capacity for physical exertion. In the one patient in whom electrocardiograph tracings were obtained during exercise with and without cytochrome C, the changes in the S-T segment induced by exercise without cytochrome C were not observed when cytochrome C had been previously injected. In addition to these observations, made in acute experiments, further observations are desirable in regard to the chronic effect of repeated injections of cytochrome C in angina pectoris. Studies which we have made in patients with intermittent claudication and Raynaud's disease indicate that the effects on muscle ischemia of the continued daily administration of cytochrome C may be quite striking. This has been borne out in early observations on patients with angina pectoris as well.

In three patients with acute coronary occlusion and myocardial infarction, 70 mg. of cytochrome C given intravenously seemed to have no immediate effect either on the electrocardiogram or on the subjective distress. In these cases the failure of cytochrome C to exert a favorable effect may be explained by the fact that it could not reach the infarcted and anoxic tissue because of the vascular occlusion.

Cytochrome C is activated by, among others, the succinic-succinic dehydrogenase system. It might, therefore, be theoretically desirable to supply, with the added cytochrome C in the tissues, an activator like succinic acid. Experiments which we have conducted with a combination of succinic acid and cytochrome C suggest that the cytochrome C effect can, in fact, be enhanced by being so combined with succinic acid.

The possible clinical uses for cytochrome C are as numerous and as varied as the clinical conditions in which anoxia is thought to play a role. In the field of pediatrics, asphyxia of the newborn immediately comes to mind. The possibility of using cytochrome C to enhance the tissue uptake of oxygen is particu-

larly intriguing in conditions associated with cerebral anoxia in view of two facts, namely, (1) that of all organs the brain is probably the most sensitive to oxygen lack; (2) that of all organs the brain has probably the greatest unsaturation of cytochrome C.

## SUMMARY

1. The effects of anoxia on the electrocardiogram can be prevented by the injection of cytochrome C.

2. Subjects seem to tolerate anoxia more easily when they have been previously injected with cytochrome C.

3. The effects of anoxia in impairing visual discrimination can be overcome by the intravenous injection of cytochrome C.

4. The effects of anoxia in slowing the cerebral functions required for code transliteration can be overcome by the injection of cytochrome C.

## REFERENCES

1. Proger, S., Aisner, M., and Squires, R. B.: The Prevention of Electrocardiographic Evidence of Myocardial Anoxemia by Chemical Means, J. Clin. Investigation **21**: 630, 1942.
2. Proger, S.: The Use of Respiratory Catalysts, Particularly Succinic Acid, in Tissue Anoxia, Bull. New England M. Center **5**: 80, 1943.
3. Proger, S., Dekaneas, D., and Schmidt, G.: The Increase of Cytochrome C Content of Organs Following Its Parenteral Injection, J. Clin. Investigation **23**: 949, 1944.
4. Proger, S.: Some Effects of Injected Cytochrome C in Animals and Man, Bull. New England M. Center **7**: 1, 1945.
5. Proger, S., and Dekaneas, D.: Some Further Observations on the Parenteral Use of Cytochrome C With Special Reference to Cerebral Anoxia and Shock, Bull. New England M. Center **7**: 149, 1945.
6. Proger, S., Dekaneas, D., and Schmidt, G.: The Effects of Anoxia and of Injected Cytochrome C on the Content of Easily Hydrolyzable Phosphorus in Rat Organs, J. Biol. Chem. **160**: 233, 1945.
7. Proger, S., Dekaneas, D., and Schmidt, G.: Some Observations on the Effect of Injected Cytochrome C in Animals, J. Clin. Investigation **24**: 864, 1945.
8. Proger, S., and Dekaneas, D.: The Use of Cytochrome C in Combating Tissue Anoxia, Science. To be published.
9. Keilin, D., and Hartree, E. J.: Preparation of Pure Cytochrome C From Heart Muscle and Some of Its Properties, Proc. Roy. Soc., London, s.B. **122**: 298, 1937.
10. McFarland, R. A., Halperin, M. H., and Niven, J. I.: Visual Thresholds as an Index of Physiological Imbalance During Anoxia, Am. J. Physiol. **142**: 328, 1944.
11. Crozier, W. M., and Holway, A. H.: Theory and Measurement of Visual Mechanisms; Visual Discriminometer Threshold Stimulus Intensity and Retinal Position, J. Gen. Physiol. **22**: 341, 1939.
12. Johnson, H. M., and Paschal, F. C.: Psychological Effects of Deprivation of Oxygen-Determination of Performance as Indicated by a New Substitution Test, Psychology **2**: 193, 1920.

# PNEUMOCOCCUS MENINGITIS IN INFANTS AND CHILDREN

## A Report on the Use of Combined Sulfonamide and Penicillin Therapy

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### INTRODUCTION

PRIOR to the advent of chemotherapy and penicillin, few recoveries from pneumococcus meningitis were reported in the pediatric literature. Waring and Smith[1] reviewed 150 cases with a 100 per cent mortality while Toomey and Roach[2] reported 157 cases with no recoveries. In Children's Hospital, Washington, D. C., there were 66 cases between 1923 and 1939 reported by Lindsay and associates[3] and Grossman,[4] and of this entire series there was only one recovery. Other reports have been similarly discouraging.

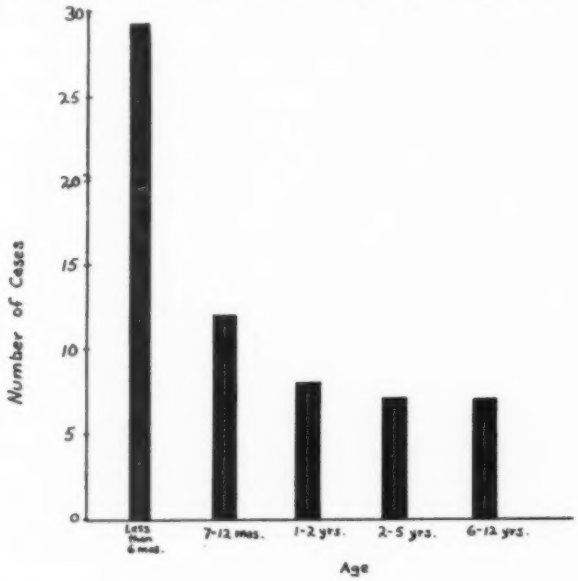
The use of sulfonamide drugs represented a considerable advance in the therapy of pneumococcus meningitis. Between 1940 and 1941 there were 16 cases of pneumococcus meningitis in Children's Hospital; 15 patients died and one recovered; the recovery occurred in a patient who received both sulfadiazine and type-specific antiserum. Of the 15 patients who died, sulfapyridine and antiserum were used in 13 cases while in the other 2, no specific therapy was employed. As a whole, our results with sulfapyridine during this interval were disappointing. In 1942, 8 patients with pneumococcus meningitis were treated, and of this series, 3 recovered and 5 died. Two of the recoveries occurred with sulfadiazine and antiserum and in one case sulfadiazine alone was used. In 1943, 14 patients with pneumococcus meningitis were treated, with 6 recoveries and 8 deaths. Of this group, therapy consisted of sulfadiazine and pneumococcus antiserum in 9 cases, sulfadiazine alone in three cases and no specific therapy in 2 cases. Of the 6 patients who recovered, all received combined sulfadiazine and pneumococcus antiserum therapy; included in the recoveries were 4 patients under 6 months of age. Two of the 6 patients who recovered had blindness and hydrocephalus as residual complications. Of the 8 patients who died, 3 were under 6 months of age, 1 was 16 months and another 20 months of age. In this group, 5 of the 8 deaths occurred within the first twenty-four hours after admission to the hospital; a sixth patient died four days after entry. These results indicated that the initiation of vigorous therapy including sulfadiazine together with pneumococcus antiserum resulted in a significant diminution in the mortality rate. However, the over-all mortality, even with the use of sulfonamide drug and type-specific antiserum, still ranged from 58 to 70 per cent from 1940 to March, 1944, both in our series and in those reported from other institutions, including the report of Hodes and associates[5] from Harriet Lane Hospital. In this regard, Dowling and associates[6] in a review of the results obtained at Gallinger Hospital, Washington, D. C., from 1938 to 1941, reported only 4 recoveries

From the Children's Hospital, Washington, D. C.

in 72 cases. All of these patients received sulfonamides, and many received additional specific antiserum. This indicated that prior to the advent of penicillin, the mortality in pneumococcus meningitis was still inordinately high, especially in infants and young children.

In April, 1944, a specific regime of therapy was adopted for pneumococcus meningitis at Children's Hospital, consisting of combined sulfadiazine and penicillin which was to be initiated as soon as the diagnosis was made. The object of the remainder of this paper is to detail the results obtained with this regime since its inception and, in addition, to compare the results with those of previous modes of therapy in the 64 patients seen at Children's Hospital since 1940.

CHART I. AGE DISTRIBUTION OF SIXTY-FOUR PATIENTS WITH PNEUMOCOCCUS MENINGITIS IN CHILDREN'S HOSPITAL FROM JANUARY, 1940, TO JUNE, 1946



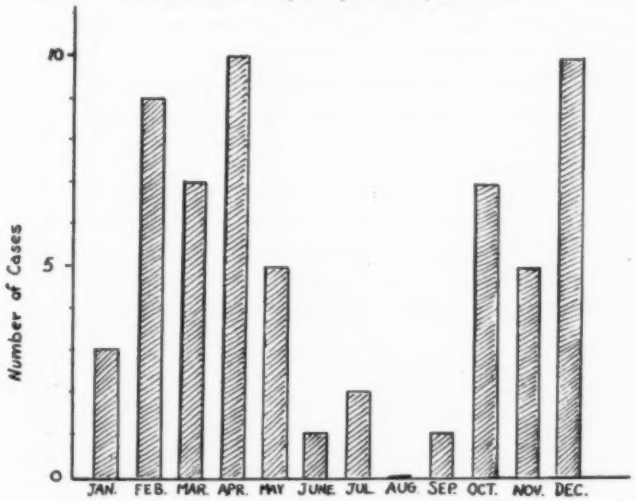

SEX, COLOR, AGE, AND SEASONAL DISTRIBUTION

The age distribution is noted in Chart I. Of the 64 patients treated since 1940, 42 were under 1 year of age, and of this number 29 were under 6 months of age. As for the seasonal distribution (Chart II), it will be seen that 58 of the 64 cases occurred between October and May, indicating that the incidence of pneumococcus meningitis coincides with the respiratory season and it is usually a disease of the late autumn, winter, and early spring. Of the 64 patients, 39 were white and 25 Negro; 35 were male and 29 female. Regarding the portal of entry, in 21 patients there was evidence of an associated pneumonia, while in 15 otitis media was present, and in 11 there was an accompanying pharyngotonsillitis. In the other 17 patients there was no obvious portal of entry.

DIAGNOSIS

*a. Clinical Aspects.*—The symptoms and signs of pneumococcus meningitis in this series are noted in Chart III. Nuchal rigidity, bulging fontanel, and convulsions were present at the time of entry in approximately one-third of the cases. Other prominent findings were lethargy and positive Brudzinski and Kernig signs in approximately one-fourth to one-third of the patients. It is to be noted, especially in the infant age group, that the presence of a bulging fontanel is an important diagnostic finding; in one-half of the 42 patients under 1 year of age a bulging fontanel was present, and in 10 cases it was the only significant finding on physical examination. Of the 21 patients having convulsions at the time of admission, all were under one year of age except

CHART II. MONTHLY DISTRIBUTION OF SIXTY-FOUR PATIENTS WITH PNEUMOCOCCUS MENINGITIS FROM JANUARY, 1940, TO JUNE, 1946




one 16-month-old-child, indicating that convulsions in the infant group is another important manifestation of meningitis. It is the practice at Children's Hospital to perform routinely a lumbar puncture on every child admitted with a history of fever and convulsions. In the infant age group, signs of meningeal irritation including nuchal rigidity and positive Brudzinski and Kernig's signs were less reliable diagnostically than in the older children. Of these three signs of meningeal irritation the Kernig sign was most equivocal and difficult to interpret. The temperature on admission in these 64 cases ranged between 99 and 107° F. with an average of 103.5° F.

In view of the variation in the signs and symptoms in meningitis, especially in the infant age group, the importance of performing lumbar punctures in any case where doubt exists cannot be stressed too strongly. This is predicated by the fact that the early manifestations of meningitis in the infant age group are often nonspecific, consisting only of fever, fretfulness, vomiting, and

diarrhea. At a time when more overt clinical manifestations of meningitis such as evidence of meningeal irritation become apparent, the disease is often well advanced.

CHART III.—CLINICAL FINDINGS ON ADMISSION IN SIXTY-FOUR CASES OF PNEUMOCOCCUS MENINGITIS

| SIGNS | NO. CASES |
|---|---|
| Nuchal rigidity | 26 |
| Bulging fontanel | 22 |
| Convulsions | 21 |
| Lethargy | 20 |
| Positive Brudzinski | 19 |
| Positive Kernig | 19 |
| Dehydration | 12 |

*b. Laboratory Diagnosis.*—In 35 of the 64 cases, pneumococcus organisms were demonstrated on smear, thus permitting the diagnosis to be made within a short time after lumbar puncture. In the remaining 29 cases the organisms were grown readily on culture. Pneumococcus typings showed that approximately one-half of the cases were represented by types 18, 14, and 6 (Chart IV). It is to be noted that often in pneumococcus meningitis the organisms are present in large number in contrast to meningococcus meningitis, where the number of bacteria is considerably less abundant on smear; however, there are exceptions to this rule. Spinal fluid examinations showed a variation in white cell counts ranging from 80 to 4,500, an average of 1,500 cells per cubic millimeter, with polymorphonuclear cells predominant. In the majority of cases the spinal fluid sugar was substantially reduced or absent, while the protein was usually elevated.

CHART IV. TYPING OF THE VARIOUS STRAINS FOUND IN SIXTY-FOUR CASES OF PNEUMOCOCCUS MENINGITIS AT CHILDREN'S HOSPITAL SINCE 1940

| STRAIN TYPE | NO. CASES |
|---|---|
| 18 | 16 |
| 14 | 8 |
| 6 | 7 |
| 7 | 5 |
| 4 | 4 |
| 15 | 2 |
| 19 | 2 |
| 12 | 2 |
| 20 | 2 |
| 3 | 2 |
| 1, 8, 9, 10, 13, 24, and 28 | 1 each |
| Undetermined | 7 |

## THERAPY

Since April, 1944, there have been 19 patients with pneumococcus meningitis who have been treated with combined penicillin and sulfadiazine; type-specific antiserum was used routinely with the first 7 patients in this series, while with the remaining 12 it was omitted. The following therapeutic regime was adopted in these 19 cases.

*a. Penicillin.*—As soon as cloudy spinal fluid was encountered, 5,000 or 10,000 units of penicillin were instilled intrathecally. The penicillin was diluted

in distilled water or saline so that 1,000 units equalled 1 c.c., and an excess of spinal fluid was withdrawn prior to intrathecal instillation. Rammelkamp and Keefer[7] have shown that in adults such a dose of penicillin intrathecally is nonirritating and will remain in therapeutic concentration in the spinal fluid from twenty-four to thirty-one hours. Our own studies in infants and children concur with this observation. In two of the cases in the present series, an increase in the number of cells in the spinal fluid was noted in the fluid withdrawn after the second lumbar puncture. This increase in pleocytosis has been known to result occasionally after intraspinal injection of penicillin, due to meningeal irritation. Penicillin given intrathecally should be introduced very slowly, either by syringe or preferably by gravity, in order to avoid any untoward central nervous system damage such as possible transverse myelitis. After intraspinal injection into the lumbar space and in the absence of blockage, penicillin readily diffuses up into the ventricles, the cerebral and subarachnoid space, and over the convexities of the cerebral cortex. Rammelkamp and Keefer[7] reported the presence of a therapeutic titer of penicillin in the spinal fluid within the skull after lumbar intrathecal instillation. Clinically, no untoward effects were noted from repeated intraspinal injections of penicillin in the present series. It is necessary to maintain careful asepsis in performing this procedure and to change the site of injection frequently in the lumbar region. The advantage of the intrathecal administration of penicillin in pneumococcus meningitis is derived from the fact that a very high concentration can be maintained at the site of infection. In none of the 19 cases was it necessary to administer penicillin into the cisterna magna or into the ventricular space directly. This latter procedure has been recommended by some authors, but the dangers, except when the process is in the most experienced hands, would preclude its widespread use. Cairns[8] recently reported a case of palsy and dysphagia following intraventricular administration of penicillin. Another contraindication to the intraventricular route is that burr holes would be necessary in children whose fontanel had already closed. Any block present in the foramina of Luschka or Magendie or in the subarachnoid space would render valueless the intracisternal mode of administration. In our experience, the lumbar subarachnoid space is the preferred site of intrathecal injection and was used repeatedly in this series. Penicillin was administered by the intrathecal route, usually on a daily schedule. The numbers of instillations ranged from one to twenty, with an average of six injections for each patient. An individual dose of 5,000 units was routinely employed in all but three instances, while the total intraspinal dose of penicillin ranged between 10,000 and 100,000 units, averaging approximately 30,000 units per patient. It was considered expedient to continue the intrathecal administration of penicillin until the spinal fluid had been sterile for from four to six days.

Simultaneously, penicillin was administered intramuscularly on a two- to three-hour schedule. With the exception of two patients, both of whom died within six hours after entry, the total amount of penicillin given intramuscularly in this series ranged between 300,000 and 14,600,000 units, with an average of 2,800,000 units per patient. This amount was administered over the

course of four to thirty days, an average of sixteen days for each patient. It was customary to continue intramuscular penicillin therapy for at least a week and preferably ten days after the temperature had returned to normal. As to the individual dose, it has been our experience that in order to achieve a good therapeutic concentration of penicillin in infants and children, it is desirable to give larger doses than one would expect on a strict weight-for-weight basis. Therefore, 10,000 to 30,000 units every two to three hours was administered, even to the infant age group.

*b. Sulfonamides.*—In the treatment of pneumococcus meningitis, in addition to penicillin, sulfonamides should be given in relatively large doses. Toward this end it has been our practice to use approximately 2 to 3 grains per pound of body weight every twenty-four hours. Before sulfonamides are started, however, an intravenous infusion of either one-sixth molar lactate or 5 per cent glucose in Hartmann's solution is given in quantities approximating 20 c.c. per pound of body weight, in view of the fact that many of the patients are dehydrated and oliguric on entry due to vomiting or inanition. Avoidance of the initial intravenous administration of sulfonamide drug diminishes to a considerable degree the instances of hematuria resulting from crystallization of the drug in the kidney when oliguria is present. Once having initiated a good urinary output, the dangers from hematuria are considerably less. The immediate infusion of crystalloid fluids such as one-sixth molar lactate or 5 per cent glucose in Hartmann's solution has the additional virtue of alkalinizing the urine and initiating the homeostatic acid-base regulatory mechanism of the kidney which is deficient in instances of oliguria and dehydration. No appreciable or significant delay is entailed in achieving an adequate blood-sulfonamide level when the subcutaneous mode of administration is employed rather than the intravenous route. Adequate levels of sulfonamide drug were usually considered to be in the range of 12 to 20 mg. per cent in our cases of pneumococcus meningitis; this was readily achieved by the administration of approximately 2 to 3 grains per pound of body weight in twenty-four hours, given by hypodermoclysis and divided into eight-hour doses. Sulfonamide drug given parenterally as the sodium salt is administered either in one-sixth molar lactate, 5 per cent glucose in Hartmann's solution, or in normal saline as a 1 per cent solution which is nonirritating under the skin. The parenteral mode of administration of sulfonamides was maintained until the patient was able to retain the drug orally. In infants where difficulty may be encountered in administering sulfadiazine in the powdered form by mouth, we have recently used sodium sulfadiazine (in 5 per cent solution) orally, and the infants seemed to tolerate it, receiving the entire dose intended.

Four patients in this series developed hematuria within the first two to four days. However, in view of the urgency of maintaining the sulfonamide drug, it was thought inadvisable to discontinue the drug at that time. Fluids were forced intravenously, by clysis and by mouth. Bicarbonate of soda was administered and the dosage of sulfadiazine was reduced to 1 to 1.5 grains per pound of body weight. In all instances, the hematuria cleared up without any

untoward complications. It would seem that hematuria per se does not constitute a cogent reason for discontinuing sulfonamide drug in cases of pneumococcus meningitis, in view of the fact that discontinuing the drug prematurely may have an untoward effect upon the course of the disease. However, each case has to be individualized. In some instances when hematuria develops, it may be possible to discontinue the drug with impunity, especially when the child is convalescent or the infection is mild. Anuria is a more definite indication for discontinuing sulfonamide therapy than hematuria. Crystalluria is a frequent finding in cases where sulfonamides are used in large doses, but does not seem to be of any real significance and certainly does not constitute an indication for discontinuing the drug. During the acute phase of the infection, it may be deemed advisable to risk the more remote possibility of kidney damage rather than fail to maintain a full measure of therapy against pneumococcus meningitis. In this series, sulfadiazine was maintained for approximately eight to twelve days after the temperature had returned to normal.

*c. Type-Specific Antiserum.*—Since the introduction of sulfonamide drugs and prior to the advent of penicillin, type-specific antiserum was used in approximately one-half of the 80 cases seen at Children's Hospital from 1938 to April, 1944. In comparing the results obtained with sulfonamides alone and combined sulfonamide-antiserum therapy (Chart V) it will be noted that only 5.3 per cent of the recoveries occurred with sulfonamides alone while 21.4 per cent of the recoveries were obtained with combined therapy, suggesting that antiserum contributed substantially to the frequency of recovery in pneumococcus meningitis.

CHART V.—A COMPARISON OF THE RESULTS OBTAINED WITH SULFONAMIDES ALONE AND SULFONAMIDES AND SERUM PRIOR TO THE USE OF PENICILLIN

| TYPE OF THERAPY | TOTAL | NUMBER RECOVERIES | DEATHS | PER CENT RECOVERIES |
|---|---|---|---|---|
| Sulfonamides alone | 38 | 2 | 36 | 5.3 |
| Sulfonamides and serum | 42 | 9 | 33 | 21.4 |
| Total | 80 | 11 | 69 | |

However, in the present series where combined sulfonamide and penicillin therapy was employed, type-specific antiserum was administered only in the first 7 consecutive cases while it was routinely omitted in the next 12 cases. In the 7 cases treated with type-specific antiserum in conjunction with sulfonamide drug and penicillin, there were 6 recoveries and 1 death. Of these 7 patients, 4 were in the infant age group (1 year and under). In the 12 cases where antiserum was omitted, there were 10 recoveries and 2 deaths; however, as will be described later, both of these fatalities occurred within six hours after hospital admission. Of these 12 patients, 7 were infants. The average severity of infection at the time of entry was roughly comparable in both those who received type-specific antiserum and in those in whom it was omitted; therefore, the element of selection was probably minimal. There appeared to be no perceptible difference in course or morbidity in the cases where serum was not used. Because this series is small, it is difficult to appraise the value

of serum as an adjunct in therapy when combined sulfonamide and penicillin is employed. It is possible that combined therapy may have minimized the need for type-specific antiserum. It would probably be safe to omit antiserum at the beginning of therapy and allow its necessity to be determined by the course of the infection.

*d. Supportive Therapy.*—Supportive measures are also indicated, including adequate amounts of fluid to combat dehydration, amino acid preparations, and plasma to repair protein deficit, as well as whole blood. All these have distinct value. The majority of the patients in the present series received at least one whole blood transfusion during the course of their illness.

*e. Heparin and Spinal Fluid Drainage.*—In 5 of the patients (Cases 10, 11, 12, 13, and 16) where it appeared that a chronic basilar meningitis was developing as indicated by varying degrees of spasticity and a viscid spinal fluid with elevated protein, it was deemed advisable to instill heparin intrathecally (1 c.c. per dose) for three or four consecutive days. Simultaneously, spinal fluid drainage was attempted with the substitution of air into the subarachnoid space. This was thought to have the virue of breaking up any small adhesions that might have occurred and maintaining free flow between the ventricles and the spinal subarachnoid space. In one instance, heparin was discontinued after xanthochromic fluid was obtained, this occurring after 40 mg. or 4 c.c. of heparin had been injected intrathecally over the course of four days. It is impossible to evaluate accurately the role of intrathecal instillation of heparin in this small series. Alexander[9] has used it in 2 cases of *Hemophilus influenzae* meningitis and Signorelli and Friedman[10] in one patient, and both reported some benefit from its use. Of 9 patients with pneumococcus and *H. influenzae* meningitis who received heparin and air intrathecally during the past year at Children's Hospital, it seemed that some improvement did follow its use. Purely on an empirical basis, it would therefore appear advisable to employ the intrathecal injection of heparin and air as a last resort in those instances where development of chronic basilar meningitis is suspected. This is especially important in cases where therapy has been instituted late and where infection has had ample time to produce walled-off pus pockets.

*f. Follow-Up Laboratory Work.*—Daily sulfonamide levels should be obtained during the first week, and for the sake of uniformity it is desirable to obtain the assay about one hour before the next dose is to be administered. The blood levels in this series were maintained between 12 and 20 mg. per cent. A daily urinalysis should be performed to watch for toxic drug effects, especially hematuria. Daily spinal fluid examinations during the acute phase of the disease are singularly helpful in permitting a rather objective evaluation of the patient's course. A decrease in the cell count and protein and an increase in the sugar content can often be construed as favorable prognostic indications. In the series of 19 cases treated with combined penicillin-sulfonamide therapy, spinal fluid cultures became negative on an average of three days after initiation of treatment. However, no penicillinase was added to these spinal fluid cultures, and

this finding may well have represented in part an inhibition of the culture growth of the organism by the penicillin already present in the spinal fluid.

It cannot be stressed too strongly that both sulfonamides and penicillin should be continued for at least eight to twelve days after the spinal fluid has become sterile.

*g. Surgical Intervention.*—As previously noted, otitis media was a frequent associated finding in this series. Resort to the judicious use of surgery in cases of complicating mastoiditis and other foci amenable to surgery is usually regarded as a therapeutic adjunct of primary importance. However, in the current series where combined sulfonamide-penicillin therapy was employed, no mastoidectomies were performed. It is still speculative whether or not our current therapy makes surgical intervention less imperative.

## RESULTS

In 19 consecutive cases of pneumococcus meningitis treated with combined sulfadiazine and penicillin, there were 3 deaths (Chart VI A).

The first fatality (Case 1) occurred in a 1-year-old infant who was admitted in April, 1944, when penicillin was still relatively unavailable. He received sulfadiazine, type-specific antiserum, and supportive therapy for the first six days after admission, and only when his condition appeared to have become critical was penicillin instituted more or less as a terminal measure. The dose was 5,000 units every three hours and he received a total of 60,000 units. The infant died on the eighth hospital day, two days after the initiation of penicillin therapy. No intrathecal penicillin was administered.

The second death occurred in a 12-year-old boy (Case 9), who was admitted to the hospital in a moribund condition after having received a skull fracture involving the anterior fossa and the cribriform plate, with complicating pneumococcic meningitis. The child, prior to entry, had received .25 grain of morphine which might have been contributory to his sudden death. He remained stuporous and died six hours after admission. One dose of penicillin intramuscularly (50,000 units) and one dose of sodium sulfadiazine were administered prior to death.

The third death (Case 19) was that of a 9-year-old girl who was comatose at the time of hospital entry and had a temperature of 106° F. She received one intrathecal dose of penicillin (10,000 units) and two intramuscular injections of 40,000 units at two-hour intervals; in addition, one parenteral dose of sodium sulfadiazine was administered. However, the child never regained consciousness and died six hours after admission.

Thus in two of the three fatalities, death occurred within six hours after admission to the hospital; the rapid terminal progression was such that it precluded an evaluation of the efficiacy of combined therapy in both cases. A fair trial of therapy would require a survival of at least twelve to twenty-four hours after its initiation before the effect could be ascertained.

CHART VI A. RESULTS OBTAINED IN NINETEEN CASES OF PNEUMOCOCCIC MENINGITIS

| CASE | NAME, AGE, RACE | SYMPTOMS AND SIGNS | DURATION OF ILLNESS BEFORE ADM. (DAYS) | PREVIOUS THERAPY | SPINAL FLUID ON ADMISSION |
|---|---|---|---|---|---|
| 1 | B. S. 12 mo. White | Critically ill; convulsions; tense fontanel; pneumonia; temperature, 103.6° F. | 3 | None | Pn.—type 14; 1,180 W.B.C. with 94% P.; sugar; less than 10 mg. % |
| 2 | F. B. 6 yr. White | Critically ill; opisthotonos; comatose; meningeal signs; temperature, 104.8° F. | 4 | None | Pn.—type 18; 270 W.B.C. with 84% P.; sugar, 20-30 mg. % |
| 3 | F. W. 5 yr. White | Acutely ill; meningeal signs; temperature 102° F. | 5 | Sulfonamide, 1 day | Pn.—type 18; 950 W.B.C. with 39% P.; sugar, 0 |
| 4 | C. B. 12 mo. Negro | Acutely ill; meningeal signs; pneumonia; temperature, 103.4° F. | 10 | Sulfonamide, 8 days | Pn.—type 6; 780 W.B.C. with 75% P.; sugar, less than 10 mg. % |
| 5 | J. T. 5 mo. Negro | Acutely ill; convulsions; dehydration; pneumonia; temperature, 104.4° F. | 4 | None | Pn.—type 28; 790 W.B.C. with 76% P.; sugar, less than 10 mg. % |
| 6 | A. E. 3 mo. Negro | Moderately ill; lethargic; otitis media; temperature, 104.4° F. | 5 | Sulfonamide, 3 days | Pn.—type 6; 156 W.B.C. with 56% P.; sugar, 40-50 mg. % |
| 7 | J. T. 13 mo. Negro | Moderately ill; pneumonia; meningeal signs; temperature, 104° F. | 2 | None | Pn.—type 18; 7,450 W.B.C. with 90% P.; sugar, 20-30 mg. % |
| 8 | D. H. 8 mo. Negro | Acutely ill; meningeal signs; bulging fontanel; pneumonia; temperature, 104.2° F. | 4 | None | Pn.—type 6; 1,500 W.B.C. with 85% P.; sugar, less than 10 mg. % |
| 9 | G. B. 12 yr. White | Critically ill; comatose; fractured skull; convulsions; temperature, 103° F. | 2 | None | Pn.—type 19; 3,320 W.B.C. with 90% P.; sugar, 40 mg. % |
| 10 | M. S. 3 mo. White | Acutely ill; listless; bulging fontanel; meningeal signs; temperature, 103° F. | 8 | None | Pn.—type 7; 1,520 W.B.C. with 85% P.; sugar, less than 10 mg. % |
| 11 | J. F. 11 mo. Negro | Acutely ill; meningeal signs; pneumonia; temperature, 105° F. | 2 | None | Pn.—type 6; 750 W.B.C. with 88% P.; sugar, 20-30 mg. % |
| 12 | D. G. 5 mo. White | Critically ill; convulsions; tense fontanel; temperature, 102.6° F. | 4 | Sulfonamide, 3 days; penicillin, 2 days | Pn.—type 7; 1,150 W.B.C. with 75% P.; sugar, 20-30 mg. % |
| 13 | L. F. 4 mo. White | Moderately ill; bulging fontanel; temperature, 105° F. | 2 | None | Pn.—type 14; 4,000 W.B.C. with 89% P.; sugar, 35 mg. % |
| 14 | W. G. 14 mo. White | Moderately ill; slight nuchal rigidity; temperature, 101.2° F. | 3 | Sulfonamide, 3 days | Pn.—type 14; 2,000 W.B.C. with 87% P.; sugar, 40-50 mg. % |

TREATED WITH COMBINED PENICILLIN AND SULFONAMIDE DRUG THERAPY*

| MODE OF THERAPY | | | | | |
|---|---|---|---|---|---|
| PENICILLIN | | | | | |
| INTRATHECAL | INTRAMUSCULAR | SULFONAMIDES | ANTI-SERUM | RESULTS | COMPLICATIONS |
| None | 5,000 u. q. 3 hr. Total—60,000 u. | Sulfadiazine Gr. 2 to 3/lb./24 hr. | 200,000 u. | D. | — |
| 5,000 u. for 11 doses Total—55,000 u. | 10,000-30,000 u. q. 3 hr. Total—1,400,000 u. | Sulfadiazine Gr. 2 to 3/lb./24 hr. | 300,000 u. | R. | Deafness |
| 10,000 u. for 1 dose | 10,000 u. q. 3 hr. Total—300,000 u. | Sulfadiazine Gr. 1 to 3/lb./24 hr. | 100,000 u. | R. | None |
| 5,000 u. for 5 doses Total—25,000 u. | 10,000 u. q. 3 hr. Total—800,000 u. | Sulfadiazine Gr. 1 to 2/lb./24 hr. | 100,000 u. | R. | Spasticity; blindness |
| 5,000 u. for 4 doses Total—20,000 u. | 10,000-20,000 u. q. 3 hr. Total—900,000 u. | Sulfadiazine Gr. 2 to 4/lb./24 hr. | 200,000 u. | R. | None |
| 5,000 u. for 4 doses Total—20,000 u. | 10,000-20,000 u. q. 3 hr. | Sulfadiazine Gr. 1 to 3/lb./24 hr. | 250,000 u. | R. | None |
| 5,000 u. for 3 doses Total—15,000 u. | Total—2,400,000 u. 10,000 u. q. 3 hr. | Sulfadiazine Gr. 2 to 3/lb./24 hr. | 50,000 u. | R. | None |
| 5,000 u. for 3 doses Total—15,000 u. | Total—760,000 u. 15,000 u. q. 3 hr. Total—1,200,000 u. | Sulfadiazine Gr. 2 to 3/lb./24 hr. | 0 | R. | None |
| None | 50,000 u.—1 dose | Sulfadiazine 1 dose | 0 | D. (6 hours after entry) | — |
| 5,000 u. for 20 doses Total—100,000 u. | 10,000-15,000 u. q. 2-3 hr. Total—5,100,000 u. | Sulfadiazine Gr. 1 to 3/lb./24 hr. | 0 | R. | Arrested hydrocephalus; spasticity |
| 5,000 u. for 6 doses Total—30,000 u. | 20,000 u. q. 2 hr. Total—3,900,000 u. | Sulfadiazine Gr. 2/lb./24 hr. | 0 | R. | None |
| 5,000 u. for 8 doses Total—40,000 u. | 20,000 u. q. 2-3 hr. Total—3,000,000 u. | Sulfadiazine Gr. 1 to 2/lb./24 hr. | 0 | R. | None |
| 5,000 u. for 8 doses Total—40,000 u. | 20,000-30,000 u. q. 2-3 hr. Total—6,800,000 u. | Sulfadiazine Gr. 2 to 3/lb./24 hr. | 0 | R. | None |
| 10,000 u. for 1 dose | 10,000 u. q. 3 hr. Total—850,000 u. | Sulfadiazine Gr. 2 to 3/lb./24 hr. | 0 | R. | None |

CHART VI A. RESULTS OBTAINED IN NINETEEN CASES OF PNEUMOCOCCIC MENINGITIS

| CASE | NAME, AGE, RACE | SYMPTOMS AND SIGNS | DURATION OF ILLNESS BEFORE ADM. (DAYS) | PREVIOUS THERAPY | SPINAL FLUID ON ADMISSION |
|---|---|---|---|---|---|
| 15 | G. R. 17 mo. White | Acutely ill; meningeal signs; tense fontanel; temperature, 103.6° F. | 9 | Sulfonamide, 3 days | Pn.—type unknown; 533 W.B.C. with 14% P.; sugar, 20-30 mg. % |
| 16 | J. J. 6 wk. Negro | Critically ill; marked spasticity and opisthotonos; temperature, 104° F. | 4 | None | Pn.—type 8; 610 W.B.C. with 93% P.; sugar, 0 |
| 17 | B. M. 9 yr. White | Moderately ill; meningeal signs; temperature, 104.2° F. | 3 | Sulfonamide, 2 days | Pn.—type unknown; 1,060 W.B.C. with 80% P.; sugar, 10 mg. % |
| 18 | P. S. 4 mo. White | Moderately ill; tense fontanel; temperature, 103.4° F. | 2 | None | Pn.—type 1; 1,400 W.B.C. with 89% P.; sugar, 45 mg. % |
| 19 | V. F. 9 yr. White | Critically ill; comatose; meningeal signs; temperature, 106° F. | 3 | None | Pn.—type 3; 232 W.B.C. with 90% P.; sugar, 10 mg. % |

*Type-specific antiserum was used in only the first seven cases.

In the 16 remaining cases it was considered that adequate combined sulfonamide drug and penicillin had been employed, and in every case recovery ensued.

It is of some interest to note the age distribution as related to the incidence of recoveries (Chart VIB). Of the 19 patients, 9 were under 1 year of age; of these, there were 7 under 6 months while the other 2 ranged from 6 to 12 months. These 9 infants all recovered in spite of the fact that the duration of illness in the infant group prior to the initiation of combined therapy ranged from two to eight days with an average of three days per patient. This assumes a degree of importance when the usually high mortality rate of this age group is considered. The reason for the hitherto high mortality in infants under 1 year has been variously attributed to a poorer antigenic response and/or greater susceptibility to pneumococcal infections. No less important, however, is the frequent delay in making an early diagnosis in infants because of the paucity of physical findings during that stage of the disease when it is more amenable to therapy.

The conclusion seems warranted that if all the adjuncts in therapy previously outlined are brought to bear as quickly and as vigorously as possible, the prognosis, even in the infant age group, is relatively good.

The youngest patient in this series was a 6-week-old Negro male whose course in the hospital follows.

The infant was admitted with a history of fever and diarrhea of six days' duration. Several episodes of vomiting and drowsiness occurred four days prior to entry. At the time of admission, he was critically ill with marked spasticity, partial opisthotonos, and coarse persistent tremors. The temperature was 104° F. Spinal tap yielded cloudy fluid

TREATED WITH COMBINED PENICILLIN AND SULFONAMIDE DRUG THERAPY*—CONT'D

| MODE OF THERAPY | | | | | |
|---|---|---|---|---|---|
| PENICILLIN | | | | | |
| INTRATHECAL | INTRAMUSCULAR | SULFONAMIDES | ANTI-SERUM | RESULTS | COMPLICATIONS |
| 5,000 u. for 2 doses Total—10,000 u. | 10,000 u. q. 3 hr. Total—720,000 u. | Sulfadiazine Gr. 2/lb./24 hr. | 0 | R. | None |
| 5,000 u. for 16 doses Total—80,000 u. | 30,000-50,000 u. q. 2 hr. Total—14,600,000 u. | Sulfadiazine Gr. 2 to 4/lb./24 hr. | 0 | R. | None |
| 5,000 u. for 2 doses Total—10,000 u. | 30,000 u. q. 3 hr. Total—2,880,000 u. | Sulfadiazine Gr. 2 to 3/lb./24 hr. | 0 | R. | None |
| 5,000 u. for 2 doses Total—10,000 u. | 20,000 u. q. 3 hr. Total—1,760,000 u. | Sulfadiazine Gr. 3/lb./24 hr. | 0 | R. | None |
| 10,000 u. for 1 dose | 40,000 u.—2 doses Total—80,000 u. | Sulfadiazine 1 dose | 0 | D. (6 hours after entry) | — |

Key: Pn., pneumococcus; W.B.C., white blood cell count; P. polymorphonuclear leucocytes; R, recovered; D, died.

containing 610 white cells with 93 per cent polymorphonuclears; sugar was absent and protein content was 60 mg. per cent. Pneumococcus (type 8) was found on smears and culture.

The child received sulfadiazine parenterally (2 to 4 grains per pound body weight) and penicillin, both intramuscularly and intrathecally. The intramuscular dose ranged from 30,000 to 50,000 every 2 hours, and a total dose of 14,600,000 units was administered over the course of four and one-half weeks during which penicillin therapy was maintained. The intrathecal dose of penicillin was 5,000 units daily and sixteen intrathecal injections were administered for a total of 80,000 units. In addition, 1 c.c. of heparin intrathecally was given on four consecutive days when it became apparent that a chronic basilar meningitis was developing. Supportive therapy included parenteral fluids, blood transfusions, oxygen, and sedation for persisting convulsions. No type-specific pneumococcus antiserum was used.

CHART VIB.—RECOVERIES BY AGE IN NINETEEN CASES OF PNEUMOCOCCUS MENINGITIS TREATED WITH COMBINED SULFONAMIDE DRUGS AND PENICILLIN*

| AGE | NUMBER CASES | NO. RECOVERIES | PER CENT RECOVERIES |
|---|---|---|---|
| Less than 6 months | 7 | 7 | 100 |
| 6 to 12 months | 2 | 2 | 100 |
| 1 to 2 years | 5 | 4 | 80 |
| 2 to 6 years | 1 | 1 | 100 |
| 6 to 12 years | 4 | 2 | 50 |
| Total | 19 | 16 | 84.2 |

*Seven of the nineteen cases received type-specific Antiserum in Addition.

A stormy course in the hospital ensued, punctuated by a complicating urinary tract infection (due to *Bacillus coli*) and persisting diarrhea. The opisthotonos and spasticity gradually disappeared, and after the first week no further convulsive seizures were noted. The spinal fluid became sterile within five days after admission and remained so during

the remainder of the hospital course. The infant was discharged ostensibly well after a six-week hospital stay. The matter of residual central nervous system damage will have to be determined by future follow-ups.

A comparison of the recoveries from pneumococcus meningitis in children under 2 years of age is made with those reported from other institutions (Chart VII); the percentage of recoveries appears to be directly proportional to the incidence of the use of combined penicillin and sulfonamide treatment, less favorable results having been obtained when penicillin alone was used. This is in keeping with Waring and Smith's[1] conclusion that penicillin alone seemed capable of curing the disease in only a relatively small percentage of cases; in other cases, it checked the course of the disease for a limited period but was unable to arrest it completely. It is difficult to say whether penicillin and sulfonamides, used in combination, act by summation or by synergistic action but, whatever the modus operandi, combined therapy is the treatment of choice in pneumococcus meningitis.

CHART VII.—ANALYSIS OF PNEUMOCOCCUS MENINGITIS IN CHILDREN UNDER TWO YEARS OF AGE WITH A COMPARISON OF THE RESULTS REPORTED FROM VARIOUS INSTITUTIONS*

| AUTHORS | NO. CASES | COMBINED PENICILLIN AND SULFONAMIDE THERAPY (%) | NO. RECOVERIES | DEATHS | PER CENT RECOVERIES | RECOVERIES WITH RESIDUAL CNS DAMAGE |
|---|---|---|---|---|---|---|
| White and associates[11] | 12 | 14 | 5 | 7 | 41.7 | 4 |
| Hutchins and Davies[12] | 14 | 64 | 9 | 5 | 64.4 | 5 |
| Waring and Smith[1] | 9 | 92 | 8 | 1 | 88.8 | 3 |
| Children's Hospital, Wash., D. C. | 14 | 100 | 13 | 1 | 92.9 | 3 |

*Note the correlation between the incidence of recoveries and the number of cases where combined penicillin and sulfonamide drug were employed.

It is of interest to compare the results obtained with the various types of therapy indicated in Chart VIII in 95 patients with pneumococcus meningitis treated at Children's Hospital since 1933. The gratifying increase in recovery rate since the advent of chemotherapy and penicillin can be clearly noted.

CHART VIII.—TYPES OF THERAPY FOR PNEUMOCOCCUS MENINGITIS BETWEEN JANUARY, 1933, AND JUNE, 1946, CHILDREN'S HOSPITAL, WASHINGTON, D. C.*

| THERAPY | TOTAL | NUMBER RECOVERIES | DEATHS | PER CENT RECOVERIES |
|---|---|---|---|---|
| Nonspecific | 16 | 0 | 16 | 0.0 |
| Serum alone | 6 | 0 | 6 | 0.0 |
| Sulfonamide alone | 21 | 2 | 19 | 9.5 |
| Sulfonamide and serum | 33 | 10 | 23 | 33.0 |
| Sulfonamides and penicillin | 12 | 10 | 2 | 83.3 |
| Sulfonamides, penicillin, and serum | 7 | 6 | 1 | 85.7 |
| Total | 95 | 28 | 67 | |

*The striking increase in the recovery rate with the advent of combined sulfonamide-penicillin therapy is clearly demonstrated.

In Chart IX, the recoveries from pneumococcus meningitis since 1940 are correlated with age and type of therapy. The 84.2 per cent recovery rate with combined sulfonamide-penicillin therapy is in striking contrast to the 25.6 per cent recovery rate obtained with sulfonamide drugs alone.

CHART IX.—RECOVERIES CORRELATED WITH AGE AND TYPE OF THERAPY IN SIXTY-TWO CASES OF PNEUMOCOCCUS MENINGITIS SINCE 1940*

| AGE | SULFONAMIDE THERAPY | | | SULFONAMIDE AND PENICILLIN THERAPY | | |
|---|---|---|---|---|---|---|
| | TOTAL NUMBER TREATED | NUMBER RECOVERIES | PER CENT RECOVERIES | TOTAL NUMBER TREATED | NUMBER RECOVERIES | PER CENT RECOVERIES |
| Up to 1 year | 31 | 6 | 19.4 | 9 | 9 | 100.0 |
| 1 to 2 years | 5 | 1 | 20.0 | 5 | 4 | 80.0 |
| 3 to 12 years | 7 | 4 | 57.1 | 5 | 3 | 62.5 |
| Total | 43 | 11 | 25.6 | 19 | 16 | 84.2 |

*The advantage of combined sulfonamide-penicillin therapy over sulfonamide drug alone is evident. Note the 100 per cent recovery rate in the infant age group when combined therapy was employed. The relatively low incidence of recovery in the 3-to 12-year age group is more apparent than real in view of the fact that the 2 deaths in this age group occurred within six hours after admission and did not constitute an adequate trial of the efficacy of combined therapy.

## COMPLICATIONS

In this series, of the 16 children who recovered, 3 had complications. One patient, a 6-year-old boy (Case 2) had residual deafness, while another child, 14 months of age (Case 4), was spastic and appeared to be blind at the time of discharge. A third child, 3 months of age (Case 10), suffered several relapses during his course in the hospital, probably due to premature discontinuation of intrathecal penicillin. This patient received heparin and air intrathecally when it became apparent that a chronic basilar meningitis had developed. A pneumoencephalogram revealed widely dilated lateral ventricles with evidence of moderately advanced hydrocephalus (Fig. 1). The infant eventually recovered from the infection after a protracted course and was discharged with a guarded prognosis. However, when seen on follow-up examination several months later, he had shown remarkable improvement in his mental and physical performance. This serves to emphasize the importance of follow-up studies on infants, who, following meningitis, have shown evidence of incipient hydrocephalus and spasticity. Some of these patients with residual central nervous system damage show considerable improvement in spite of the poor prognosis which is usually entertained at the time of discharge from the hospital. As Hartmann and associates[13] point out, hydrocephalus following meningitis may be due to the failure of absorption of spinal fluid over the cortex because of inflamed meninges, and therefore may be transient in some cases with subsequent regression of the dilatation of ventricles as absorption approaches normal.

It is to be noted that 2 of the 3 patients with complications were ill for eight days before the diagnosis was made and treatment instituted. This serves to re-emphasize the importance of early diagnosis if full recovery without central nervous system sequelae is to be expected.

It is well known that pneumococcus meningitis characteristically produces a viscid exudate of fibrin and pus over the entire brain surface and may readily produce an adhesive arachnoiditis involving the foramina of Luschka and Magendie. This may act as a focus for relapse, and the pus pockets formed may prevent the penicillin from coming in intimate contact with the organ-

isms. The only adequate way of preventing this unfortunate complication is to begin vigorous treatment before the formation of this thick plastic exudate.

The practice of having a bottle of penicillin available at the bedside at the time of initial lumbar puncture has been adopted at Children's Hospital in any case where meningitis is suspected. In the event that the spinal tap yields turbid fluid, penicillin is immediately instilled intraspinally before the nature of the organism is determined. This is based on the premise that it is more important to institute prompt and vigorous therapy in meningitis in view of its gravity than to await a bacteriologic diagnosis before initiating therapy.

Fig. 1.—M. S. (Case 10), showing widely dilated ventricles in pneumoencephalogram.

There are no clinical signs which enable one to distinguish one type of pyogenic meningitis from another except for the presence of petechiae in the meningococcus type. In addition, it occasionally happens that because of excessive decolorization or poor staining, pneumococcus may be mistaken for meningococcus and vice versa. Also in those cases where *H. influenzae* organisms are present in very small numbers with the predominance of coccal forms, there is the possibility of confusing these forms with either meningococcus or pneumococcus. Intrathecal administration of penicillin is indicated in all types of coccal meningitis and the only instance where its use would be without especial value is *H. influenzae* meningitis. The important consideration, however, is

that vigorous therapy has been instituted quickly if the organism proves to be either pneumococcus or meningococcus. We have all experienced instances where the stained smear was equivocal as to the etiological organism, and where it was necessary to await the results of culture which would not be forthcoming for from twenty-four to forty-eight hours. Such a delay would contribute to a less favorable prognosis since the outcome in meningitis is in no small part predicated by the rapidity with which adequate therapy is instituted.

### THE NECESSITY OF INTRATHECAL ADMINISTRATION OF PENICILLIN

It is well known that sulfadiazine breaches the blood-brain barrier adequately, and it has been found that the spinal fluid level of sulfadiazine is approximately 60 per cent of the blood level. However, the diffusion of penicillin into the spinal fluid following parenteral administration has been the subject of some controversy in the recent literature. Rammelkamp and Keefer[7] reported that after intravenous administration of penicillin to normal subjects, no demonstrable penicillin was detected in the spinal fluid, indicating that the penicillin administered parenterally failed to cross the arachnoid barrier. These authors suggested that the intraspinal administration of penicillin in meningitis was indicated. Orey and associates[14] similarly reported that no detectable penicillin was present in the spinal fluid following injections of 20,000 to 60,000 units intramuscularly, while McDermott and Nelson[15] administered up to 500,000 units of penicillin intramuscularly and failed to obtain significant titers of penicillin in the spinal fluid. Schwemlein and associates[16] gave massive doses of penicillin parenterally, ranging between 10,000,000 to 25,000,000 units daily, in early syphilis, and found therapeutic spinal fluid levels in the majority of instances. However, this dose is far in excess of the dose usually required in pneumococcus meningitis. On the other hand, Rosenberg and Sylvester[17] administered a comparatively small dose of 20,000 to 40,000 units both intravenously and intramuscularly to 8 subjects with pyogenic meningitis and noted spinal fluid levels ranging from .03 to .35 Florey units per cubic centimeter 60 to 140 minutes later, suggesting that penicillin may be effective in the treatment of meningitis without supplementary intrathecal administration. According to these investigators, the explanation for this disparity might possibly be attributable to the more ready passage of penicillin into the subarachnoid space in the presence of inflamed meninges. The problem has certain practical applications because of the desirability of achieving an adequate spinal fluid level of penicillin at the site of the infection; if this could be achieved by the parenteral route alone, it would preclude the necessity of simultaneous intrathecal administration of penicillin in the treatment of meningitis. Pilcher and Meecham[18] have demonstrated that parenteral administration of penicillin without intrathecal administration was inadequate in experimentally induced pneumococcus meningitis in dogs.

A series of penicillin diffusion studies were performed at Children's Hospital to determine whether therapeutic concentrations of penicillin in the spinal fluid could be obtained when varying dosages were given intramuscu-

larly to both normal infants and children and those with inflamed meninges. In addition, an attempt was made to compare the spinal fluid penicillin levels after combined intrathecal and parenteral injections with those obtained after parenteral administration alone.

In the first part of this study, the subjects included 4 patients with tuberculous meningitis, 1 patient with pneumococcus meningitis and 5 with cerebral agenesis without inflamed meninges. These patients weighed between 16 and 60 pounds and the dosage given intramuscularly varied between 10,000 and 50,000 units. Spinal fluid assays were performed one, two, and three hours, respectively, after the intramuscular injection of the penicillin.

CHART X.—PENICILLIN SPINAL FLUID LEVELS AT ONE- TO THREE-HOUR INTERVALS AFTER INTRAMUSCULAR INJECTION OF VARIOUS DOSAGES

| SUBJECT | WEIGHT (LB.) | DIAGNOSIS | PENICILLIN DOSE I.M. (UNITS) | SPINAL FLUID PENICILLIN LEVELS AFTER I.M. INJECTION (FLOREY UNITS/C.C.) | | |
|---|---|---|---|---|---|---|
| | | | | 1 HOUR | 2 HOURS | 3 HOURS |
| 1 | 16 | Cerebral agenesis | 10,000 | 0 | 0 | 0 |
| 1 | 16 | Cerebral agenesis | 10,000 | 0 | 0 | 0 |
| 2 | 23 | Cerebral agenesis | 10,000 | 0 | 0 | 0 |
| 2 | 23 | Cerebral agenesis | 10,000 | 0 | 0 | 0 |
| 3 | 30 | Tuberculous meningitis | 25,000 | 0 | 0 | 0 |
| 4 | 35 | Tuberculous meningitis | 25,000 | 0 | 0 | 0 |
| 5 | 38 | Tuberculous meningitis | 25,000 | .078 | .039 | .020 |
| 6 | 60 | Pneumococcus meningitis | 30,000 | | 0 | |
| 7 | 32 | Tuberculous meningitis | 50,000 | .156 | .078 | .039 |
| 8 | 25 | Cerebral agenesis | 50,000 | 0 | 0 | 0 |
| 9 | 30 | Cerebral agenesis | 50,000 | 0 | 0 | 0 |
| 10 | 34 | Cerebral agenesis | 50,000 | 0 | 0 | 0 |

It will be noted in Chart X that in only 2 out of 10 cases were significant spinal fluid titers of penicillin noted after intramuscular injection. One of these, a child with tuberculous meningitis (Subject 5) after 25,000 units of penicillin intramuscularly, showed a titer of .078, .039, and .02 Florey units, respectively, at the end of one, two, and three hours. The second child, also with tuberculous meningitis (Subject 7) showed a therapeutic concentration in the spinal fluid after 50,000 units intramuscularly. It was interesting to note that the patient with pneumococcus meningitis (Subject 6) showed no demonstrable spinal fluid titer of penicillin after 30,000 units intramuscularly. These results would seem to indicate that infants and children, like adults, show poor diffusion of penicillin across the blood-brain barrier, and in order to insure adequate therapeutic concentrations in the spinal fluid it is not possible to rely upon the parenteral administration alone.

In the second portion of this study, an attempt was made to determine the longevity of a demonstrable penicillin titer in the spinal fluid after one dose intrathecally in children. Toward this end, 5,000 units were instilled intraspinally in 4 subjects and spinal fluid levels were determined at intervals ranging between eleven and twenty-four hours after the intrathecal injection (Chart XI). It was found that in the 4 cases, a titer ranging from .039 to 0.078 Florey units was present at the end of the intervals noted. This is essentially in agreement with the results obtained in adults by Rammelkamp and Keefer[7]

who found therapeutic concentrations still present at the end of twenty-four to thirty-one hours after a single intrathecal injection of approximately 10,000 units.

CHART XI.—ILLUSTRATING SPINAL FLUID PENICILLIN LEVELS AT VARIOUS TIME INTERVALS FOLLOWING INTRATHECAL ADMINISTRATION OF PENICILLIN

| SUBJECT | WEIGHT | INTRATHECAL DOSE | TIME INTERVAL AFTER PENICILLIN ADMINISTRATION | SPINAL FLUID LEVEL (FLOREY UNITS/C.C.) |
|---|---|---|---|---|
| 1 | 20 | 5,000 units | 11 hours | .039 |
| 2 | 25 | 5,000 units | 12 hours | .078 |
| 3 | 28 | 5,000 units | 24 hours | .039 |
| 4 | 22 | 5,000 units | 24 hours | .078 |

In the third portion of this study, spinal fluid penicillin assays were performed on 5 children with pyogenic meningitis during the course of therapy. These children were receiving a daily intrathecal injection of penicillin of either 5,000 or 10,000 units, together with 20,000 units of penicillin intramuscularly every two hours. The spinal fluid assays were performed at intervals of nine to twenty-four hours after the institution of therapy to determine the nature of the levels obtained with this recommended mode of penicillin administration, i.e., a combination of intrathecal and intramuscular injections. It was found that in all cases adequate titers were present at the end of the stated intervals, ranging from .039 to .312 Florey units per cubic centimeter (Chart XII). This would indicate that probably only one intrathecal dose of penicillin is required per day in infants and children.

CHART XII.—ILLUSTRATING SPINAL FLUID PENICILLIN LEVELS AT VARIOUS TIME INTERVALS FOLLOWING BOTH INTRATHECAL AND INTRAMUSCULAR ADMINISTRATION OF PENICILLIN

| SUBJECT | WEIGHT (LB.) | DIAGNOSIS | PENICILLIN (UNITS) | | TIME INTERVAL (HR.) | SPINAL FLUID LEVEL (FLOREY UNITS/C.C.) |
|---|---|---|---|---|---|---|
| | | | INTRATHECAL | INTRAMUSCULAR (Q 2 HR.) | | |
| 1 | 30 | Pneumococcus meningitis | 5,000 | 20,000 | 9 | .078 |
| 2 | 22 | Pneumococcus meningitis | 5,000 | 20,000 | 12 | .312 |
| 3 | 18 | Pneumococcus meningitis | 5,000 | 20,000 | 24 | .039 |
| 4 | 24 | Meningococcus meningitis | 5,000 | 20,000 | 24 | .312 |
| 5 | 16 | Meningococcus meningitis | 10,000 | 20,000 | 24 | .156 |

The conclusion seems warranted that combined intrathecal and intramuscular injections of penicillin in children offers the optimal means of obtaining satisfactory concentrations of penicillin in the spinal fluid in all cases, and would be the method of choice in treating penicillin-susceptible pyogenic meningitis.

## CONCLUSIONS

1. Nineteen infants and children with pneumococcus meningitis were treated with combined sulfonamide and penicillin therapy. Of this number, 16 recovered and 3 died. Two of the deaths occurred within six hours after entry. Three of the patients who recovered showed residual central nervous system sequelae.

2. Diffusion studies performed on infants and children indicate that penicillin should be administered both intramuscularly and intrathecally to achieve therapeutic spinal fluid penicillin concentrations in meningitis.

3. Sulfadiazine was used in conjunction with penicillin in the present series. The combination of both drugs appears to offer definite advantages over penicillin alone. Therapy should be continued for at least eight to twelve days after sterilization of the spinal fluid.

4. Of the 19 patients receiving combined sulfonamide-penicillin therapy, type-specific antiserum was administered only to the first 7 patients while it was routinely omitted to the next 12. Of the 7 receiving antiserum, there were 6 recoveries and 1 death, while in the 12 where antiserum was omitted, there were 10 recoveries and 2 deaths. Because the series is small, it is difficult to appraise the value of antiserum as an adjunct in current therapy. It is possible that combined sulfonamide-penicillin treatment may have minimized the need for type-specific antiserum.

5. Heparin was administered intraspinally in cases where chronic basilar meningitis developed, and was thought to have some value in the treatment of this complication.

6. The importance of the early institution of therapy in pneumococcus meningitis cannot be overemphasized. If all the measures in present-day therapy are brought to bear as quickly and as vigorously as possible, the prognosis, even in the infant age group, is relatively good.

We are greatly indebted to Dr. E. Clarence Rice for his invaluable help in the supervision of the treatment of these patients. We also wish to express our appreciation to Drs. Joseph S. Wall and P. A. McLendon for their helpful suggestions and advice. Dr. Morton Johan and Miss Miriam Leetch rendered valuable aid in the accumulation of data for this paper.

## REFERENCES

1. Waring, A. J., and Smith, M. H. D.: Combined Penicillin and Sulfonamide Therapy in the Treatment of Pneumococcic Meningitis, J. A. M. A. **126**: 418, 1944.
2. Toomey, J. A., and Roach, F. E.: Pneumococcus Meningitis, Ohio State M. J. **35**: 841, 1939.
3. Lindsay, J. W., Rice, C. E., and Selinger, M. A.: Meningitis in Children—A Review of 331 Cases, Med. Ann. District of Columbia **6**: 231, 1935.
4. Grossman, A. M.: Pneumococcic Meningitis in a Three Months Old Infant With Recovery, Arch. Pediat. **57**: 355, 1940.
5. Hodes, H. L., Smith, M. H. D., and Ickes, H. J.: Sixty Cases of Pneumococcic Meningitis Treated With Sulfonamides, J. A. M. A. **121**: 1334, 1943.
6. Dowling, H. F., Dauer, C. G., Feldman, H. A., and Hartman, C. R.: Pneumococcal Meningitis: A Study of Seventy-Two Cases, New Eng. J. Med. **226**: 1015, 1942.
7. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425, 1943.
8. Cairns, H., Duthie, E. S., Lewin, W. S., and Smith, H. V.: Pneumococcal Meningitis Treated With Penicillin, Lancet **1**: 655, 1944.
9. Alexander, H. E.: Treatment of Type B Hemophilus Influenza Meningitis, J. PEDIAT. **25**: 517, 1944.
10. Signorelli, J. J., and Friedman, L. L.: Penicillin and Heparin in the Treatment of Pneumococcal Meningitis: Case Report, South. M. J. **38**: 776, 1945.
11. White, W. L., Murphy, F. D., Lockwood, J. S., and Flippin, H. F.: Penicillin in the Treatment of Pneumococcal, Streptococcal and Staphylococcal Meningitis, Am. J. M. Sc. **210**: 1, 1945.
12. Hutchins, G., and Davies, J. A. V.: Penicillin Treatment of Pneumococcus Meningitis in Infants, J. PEDIAT. **27**: 505, 1945.

13. Hartmann, A. H., Love, F. M., Wolff, D., and Kendall, B. S.: Diagnosis and Management of Severe Infections in Infants and Children: A Review of Experiences Since the Introduction of Sulfonamide Therapy, Pneumococcus Meningitis, J. PEDIAT. **27**: 118, 1945.
14. Orey, E. M., Meads, M., Brown, B., Wilcox, C., and Finland, M.: Penicillin Levels in Serum and in Some Body Fluids During Systemic and Local Therapy, J. Lab. & Clin. Med. **30**: 809, 1945.
15. McDermott, W., and Nelson, R. A.: The Transfer of Penicillin Into the Cerebrospinal Fluid Following Parenteral Administration, Am. J. Syph., Gonor., & Ven. Dis. **29**: 403, 1945.
16. Schwemlein, G. X., Barton, R. L., Bauer, J. J., Lowe, L., Bundesen, H. N., and Craig, R. M.: Penicillin in Spinal Fluid After Intravenous Administration, J. A. M. A. **130**: 340, 1946.
17. Rosenberg, D. H., and Sylvester, J. C.: The Excretion of Penicillin in the Spinal Fluid in Meningitis, Science **100**: 132, 1944.
18. Pilcher, C., and Meacham, W. F.: The Treatment of Penumococcal Meningitis by Intrathecal Administration of Penicillin, J. Neurosurg. **1**: 76, 1944.

# INTRAVENOUS ALIMENTATION OF INFANTS

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VENOCLYSIS for restoration of hydration and electrolyte balance and maintenance of fluid equilibrium for periods of two or three days and occasionally for longer periods of time has become a part of everyday pediatric practice. No attempt is usually made to provide a sufficient caloric intake during such periods. Increased understanding of metabolic changes in starvation and dehydration, increased availability of sources of nitrogen such as plasma and casein hydrolysates, and improved methods in technique of venoclysis have made adequate alimentation for extended periods of time by means of continuous intravenous clysis both desirable and practicable. The first reports of the successful employment of long periods of parenteral alimentation using, in most instances, casein hydrolysates combined with solutions of glucose, electrolyte, and vitamins, were made by surgeons and concerned adult patients. In most instances, one or more infusions over a period of several hours were given daily. Elman[1] in 1940 reported in detail on eight cases in which no food was given by mouth, but nitrogen retention was achieved or nitrogen loss greatly decreased over periods up to fifteen days by the use of daily injections of a maximum of 9.6 Gm. of nitrogen given as casein hydrolysate, and enough glucose to bring the caloric intake to a maximum of 1,600 calories. Brunschwig and associates[2] markedly reduced the nitrogen loss in three patients for periods of twenty-three days by intravenous alimentation alone. He maintained one patient in positive nitrogen balance for a period of ten days by the use of 3 Gm. of protein and thirty-five calories per kilogram of body weight. A second patient[3] was maintained in positive nitrogen balance and a weight gain achieved by the use of fat, glucose, and an amino acid mixture administered intravenously for seventeen days. Recently, Brunschwig and associates[4] reported a period of eight weeks of successful intravenous nutrition with casein hydrolysate, dextrose, saline, and vitamins. The patient remained in excellent health but lost 12.5 kg. of weight during the period of withdrawal of oral feeding. In infants, the small caliber of the veins, the great difficulty of preserving asepsis, and the marked lability of fluid and mineral equilibrium make the procedure technically much more difficult than it is in adults. Continuous venoclysis almost always has to be employed for as long as the parenteral alimentation continues, and different veins must be used every few days because of thrombosis of the vein and swelling of the adjacent tissues. Hartmann and his co-workers[5] reported successful intravenous alimentation in infants for periods of three days. They maintained a 6-year-old girl with tetanus in a good state of nutrition for fourteen days, during which time she lost only 0.5 kg. of weight. Helfrick and Abelson[6] gave complete intravenous feeding to a marantic

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infant ill with Hirschsprung's disease. They used fat, carbohydrate, and an amino acid mixture. At the end of five days the fat pads in the cheeks and fat over the ribs had returned and the general nutrition was markedly improved. The baby was able to take sufficient food by mouth to maintain his improved nutrition after this time.

This report deals with experience acquired during the last year and a half with the administration to infants by venoclysis of all, or the majority of, the needed elements of nutrition for periods up to fifteen days. Most of the children suffered from chronic or recurrent diarrhea and vomiting. The aim was to supply adequate fluid and salts, and at least maintenance amounts of calories and protein. Of necessity, somewhat arbitrary figures had to be chosen as representing basal requirements. A total fluid intake of 150 c.c., 50 calories, and 2 Gm. of protein per kilogram of body weight was elected. The saline value was calculated on the basis of Butler's figures[7] as 80 c.c., with an addition of 5 c.c. for each kilogram of body weight. In malnourished infants or those in whom clyses were continued for long periods of time, the attempt was made to furnish sufficient protein and calories to produce actual weight gain. To such infants were given amounts of protein and calories approaching, or at times exceeding, those usually contained in formula feedings, that is, two or three times the minimal standard. Vitamins were generously supplied throughout. Fat was not provided. In dehydrated infants, information on electrolyte and total osmotic equilibrium was obtained by means of carbon dioxide, chloride, and nonprotein nitrogen determinations. These were made at the outset of therapy and repeated as often as indications arose. Such determinations are of particular importance in cases of diarrhea, in view of the wide variety of patterns of electrolyte and osmotic derangements which are apt to be encountered. The type of fluid administration was adjusted to correct imbalances where found. Upper limits were not set for fluid intake, as we found that no harm ensued from the administration of large amounts of fluid, provided that salt intake was controlled.

In order to avoid the untoward effects of excessive electrolyte administration, the attempt was made to provide the lowest amount of salt compatible with good hydration of the infants. Since under such a plan the chloride rather than the sodium intake becomes the limiting factor, all estimates of the salt content of parenteral fluids were based on their chloride content. Physiological saline was taken as the basis of calculation. In this solution, sodium and chloride contents are equal. In plasma, particularly when citrated, the chloride value is close to one-half that in physiological saline. Sodium bicarbonate and lactate which do not contain chloride were not considered in these calculations.

In the first twenty-four hours, depending on the degree of hydration, saline-containing fluid in amounts equal to 5 to 10 per cent of the body weight in addition to the basal requirement was given. Subsequently, when diarrhea continued, one and one-half to two times the basal amount of electrolyte was supplied. To premature and very young infants in whom high chloride values in the plasma were observed, probably owing to small loss of chloride with diarrheal stools, less salt-containing fluid was given for correction of dehydration and

maintenance. Initially, in order to avoid embarrassment of the circulation of severely dehydrated patients by the use of hypertonic solutions, 50 to 100 c.c. of physiological saline were administered rapidly. The acidosis was then corrected by 3.7 per cent sodium bicarbonate solution. In patients with mild acidosis, sodium lactate was used when correction was indicated. In most cases blood, plasma, casein hydrolysate, and hypertonic solutions of glucose or glucose in saline were administered by means of a slow intravenous drip only when dehydration was largely overcome. In cases of severe circulatory collapse, extreme malnutrition, or anemia, blood and plasma were occasionally given in the first twenty-four hours. The frequent occurrence of hypocalcemia with attendant symptoms during the postacidotic phase, a subject to be discussed in a subsequent paper, led to the use of oral or parenteral calcium therapy.

CHART I. SUMMARY OF INTAKE OF FLUIDS, CALORIES, SALT, AND PROTEIN OF PATIENTS ON PARTIAL OR TOTAL PARENTERAL THERAPY

Directions:
Enter cubic centimeters of oral, subcutaneous, and intravenous intake in upper left corner of appropriate box.
Enter calories in lower right corner.*

| DATE | FOODS AND BEVERAGES† C.C./CAL. | $NaHCO_3$ LACT. C.C. | GLUCOSE IN WATER‡ C.C./CAL. | GLUCOSE IN SALINE§ C.C./CAL. | PHYSIOLOGICAL SALINE C.C. | PLASMA BLOOD C.C./CAL. | AMIGEN IN GLUCOSE C.C./CAL. | TOTAL INTAKE | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | FLUID C.C./CAL. | SALINE VALUE§ C.C. | PROTEIN‖ GM. |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

*Calories: 5 per cent glucose, 0.2 × cubic centimeters; 10 per cent glucose, 0.4 × cubic centimeters; amigen, 0.6 × cubic centimeters; plasma, blood, 0.2 × cubic centimeters.

†Enter in foods and beverages column all intake such as formula, tea, fruit juices, broth, but not glucose in water or saline.

‡Enter all glucose, whether administered orally or parenterally.

§Enter in saline value column the sum of: cubic centimeters of saline; cubic centimeters of glucose in saline; 0.5 × cubic centimeters of plasma, blood.

‖Protein intake in grams, 0.05 × cubic centimeters of plasma, blood, amigen; also ingested protein.

It may be of interest to list the solutions used in the management of the patients. They included a 3.7 per cent solution of sodium bicarbonate or a one-sixth molar sodium lactate solution to correct acidosis; normal saline, 5 and 10 per cent solutions of glucose or glucose in saline, blood, plasma, and a 5 per cent casein hydrolysate solution in 10 per cent glucose* to supply salts, fluids, calories, and nitrogen, and to restore and maintain circulatory volume.

A fairly simple fluid sheet, devised to provide a summary of the daily intake of the infant, is shown in Chart I. The house officer charts on this sheet each

*The use of a closed system of fluid administration and rigid precautions against contamination were found necessary in the use of this solution, as it is an excellent culture medium for bacteria.

day the amounts of fluid, saline, calories, and protein the baby has received during the past twenty-four hours. In the first column is recorded in cubic centimeters the oral intake of foods and beverages; in the second, the cubic centimeters of sodium bicarbonate or lactate solution; in the third and fourth, the amount of glucose in water and in saline; in the fifth, the cubic centimeters of physiological saline (0.9 per cent); in the sixth, plasma and whole blood; and finally, casein hydrolysate solution. The last three columns are a summary of the intake for the day. For saline values the oral intake in the food is disregarded and only the amounts administered as normal saline, glucose in saline, and that included in blood and plasma are totaled. One-half the volume of blood and plasma is calculated as saline. The total protein includes the oral intake and that given as plasma, whole blood, and casein hydrolysate solution; for these three a protein concentration of 5 per cent is assumed. In the lower right half of the column the appropriate calories are entered. These are totaled and entered in the first column of the summary below the diagonal. After examining the patient and reviewing the record, the house officer is in a position to plan the fluid management for the next day.

## CASE REPORTS

Charts II to XII are a graphic portrayal of experience based on this scheme. Nine represent cases of chronic diarrhea and two, cases of inability to ingest food. Supplemental saline, protein, calories, and total fluids are entered in separate rows. The days are shown in figures on the abscissa. The distance above the base line represents the total intake for the day. The oral intake is blocked off below in black, while the parenteral intake is represented by the white portion above. The figures nearest to the ordinates indicate the total amounts, the second set of figures to the left, the amounts per kilogram of body weight. A broken line has been drawn across each row to show the daily maintenance requirement for each child, calculated according to his body weight. The weight of the child is recorded at the top of the chart.

CASE 1.—H. R., a 7-month-old infant, had been ill for one week with high fever and a slight cough. The cough and fever continued for seven weeks after admission, although no cause for either was ever found. Five days after admission he developed a mild diarrhea, vomited, and refused food. Stool cultures were negative except for the presence of atypical colon bacilli. He lost 1.5 kg. of weight in a period of two weeks. A period of temporary starvation with parenteral fluid therapy resulted in improvement, but diarrhea and vomiting recurred as soon as oral feedings were resumed. He became acidotic. The acidosis and dehydration were corrected with sodium bicarbonate and saline, and the long period of parenteral therapy shown in Chart II was begun. He was starved for two days, small feedings were tried for the next three days without success, and he was then starved for five days, with all food and fluid given parenterally. At the end of this time oral feeding was cautiously resumed while venoclysis was continued. There was no vomiting or increase in diarrhea on this occasion but the appetite was poor. As the diarrhea abated toward the end of the period he developed hypocalcemia and was therefore treated with calcium.

The fever and slight cough continued for four more weeks but diarrhea did not recur, the patient ate well and gained slowly. When seen for the last time at the age of one year he weighed 11 kg. and was healthy and mentally alert.

This, the first experience with a long period of parenteral therapy, was undertaken before the adoption of a fluid summary sheet. One sees that too little saline and total fluid were given the majority of the time. The irregularity of protein intake is explained by the fact that the casein hydrolysate solution was

Chart II.

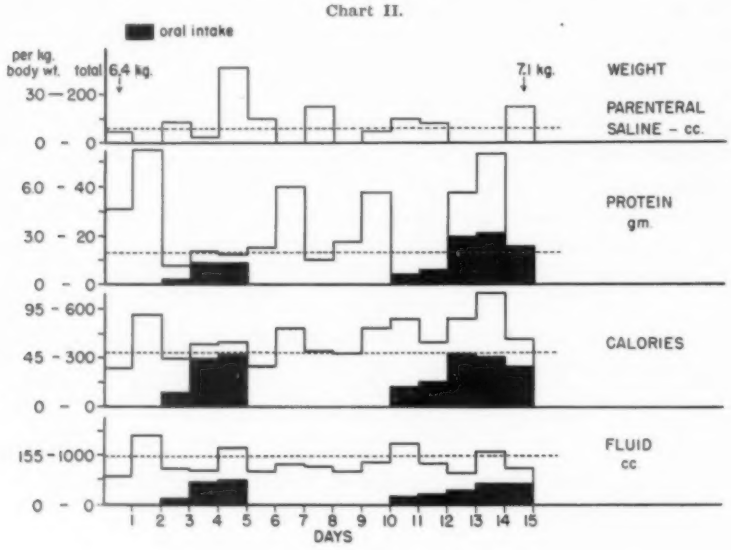
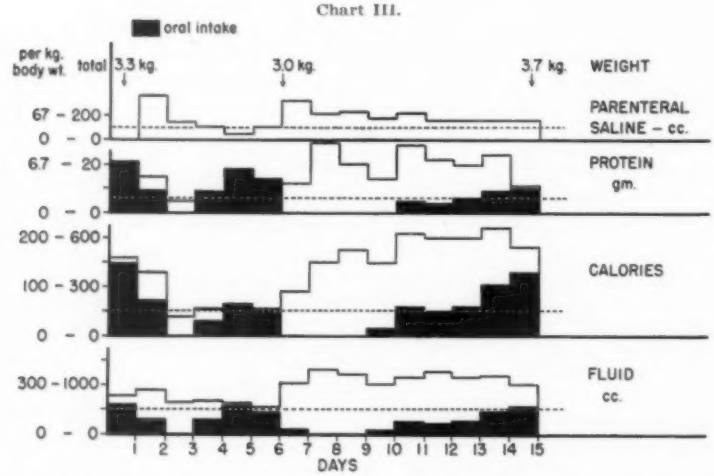



Chart III.

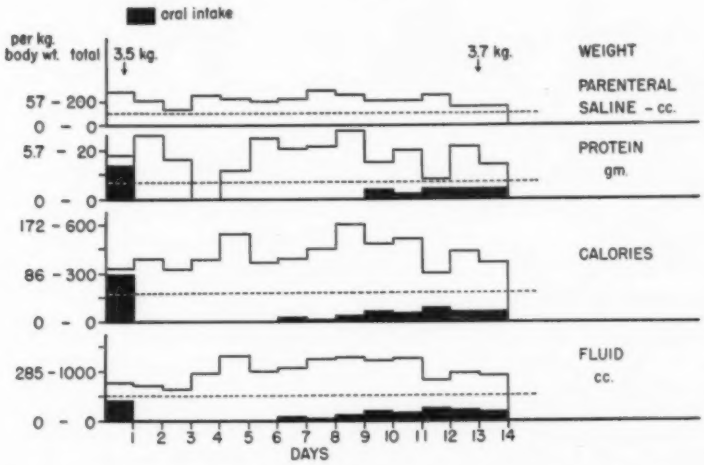



at this time supplied in one-liter bottles and that a whole flask was administered at one time. The patient's nonprotein nitrogen was elevated throughout the period, probably because of his low fluid intake and fever. He gained 0.7 kg. while on venoclysis.

CASE 2.—D. A., an infant 5 weeks of age, developed diarrhea and vomiting three days before admission. On admission he appeared undernourished and dehydrated. He weighed 0.3 kg. less than his birth weight. A short period of starvation and venoclysis was followed by ten days of moderate improvement, following which he again developed diarrhea and became dehydrated. Chart III begins with the last day of his oral feedings. A second two-day period of starvation with correction by saline and the administration of some plasma and glucose was followed by a second attempt at oral feeding which resulted in diarrhea, vomiting, and refusal of food, and led to dehydration and acidosis. These were corrected with saline and sodium bicarbonate solution, and the patient was maintained on venoclysis for nine more days with gradual resumption of oral feedings after four days. At the beginning of this last nine-day period he looked moribund and had hypocalcemia. Treatment with calcium, potassium, and phosphorus was given with apparent benefit. The stool culture at this time was positive for *Proteus morganii*. The patient gained 0.4 kilogram while on parenteral therapy. Thrombophlebitis occurred in both legs but fortunately healed well. The patient remained in the hospital one more month, during which time he suffered two slight relapses. He was discharged well.

The fluid and chloride intake were adequate and evenly distributed. The resumption of oral feedings while venoclysis is being continued has proved far more satisfactory in cases of chronic diarrhea than the abrupt cessation of venoclysis at the time when oral feeding is resumed. The failure of the first and second attempts at feeding and the success of the third illustrates this point.

Chart IV.

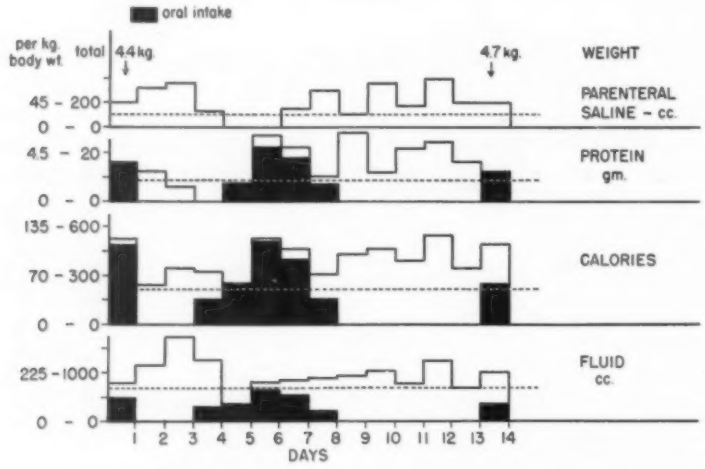



CASE 3.—G. A., a 2-month-old infant who had never eaten well since birth, began vomiting one week before admission. Five days later diarrhea commenced and on admission he weighed 0.5 kg. less than his birth weight. He was put on continuous venoclysis for eighty-four hours before his diarrhea stopped. It recurred with the resumption of oral feeding, and another period of thirty-six hours of parenteral therapy was given. Diarrhea, vomiting, and refusal of food recurred a second time when food was given. Chart IV starts with the last day of his oral feedings when his dehydration was corrected with saline. He was then maintained on venoclysis alone for five days, after which time food was started and gradually increased in amount. During this time diarrhea never ceased, although it lessened in severity.

*P. morganii* was cultured from the stools. The infant developed hypocalcemia and hypoprothrombinemia with hemorrhagic manifestations, for which conditions he was treated. At the end of the period he had a rise in temperature and became jaundiced. It was discovered that he had a large abscess at the site of the last venipuncture and septicemia, both caused by *Aerobacter aerogenes*. Surgery and streptomycin cleared up the infection. Unfortunately his subsequent course was marred by several complications unrelated to the parenteral therapy illustrated in the chart.

The management of the parenteral fluids appears on the whole satisfactory. The casein hydrolysate solution in use at this time did not contain any mercurial antiseptic (Merthiolate). Its contamination was undoubtedly responsible for the sepsis, since *A. aerogenes* was cultured from the casein hydrolysate solution itself.

Chart V.




CASE 4.—C. N., a 9-month-old baby, had pertussis at 3 months of age and was admitted to another hospital at 7 months of age for diarrhea. His weight gain had never been sufficient. Diarrhea and vomiting started one week before admission. The stools were liquid and streaked with blood. Stool cultures were positive for *Shigella paradysenteriae* and *P. morganii*. He was treated with parenteral fluids and sulfadiazine and received a skimmed milk formula for nine days but lost his appetite and began to have almost continuous green liquid stools. Chart V starts with his last day on formula. His acidosis was corrected and he was put on exclusive venoclysis for three days, but when oral intake was resumed he vomited and the diarrhea grew worse. Venoclysis was started again. The child gained 0.3 kg. while on intravenous alimentation. Hypocalcemia developed as the diarrhea stopped. When feedings were resumed at the end of five days he did exceedingly well. Since discharge he has improved both physically and mentally.

This was a smooth-running clysis except for too early resumption of oral feeding at first.

CASE 5.—A. M., a 3-month-old infant, had never done well. Diarrhea and vomiting began three days before admission. He was moderately dehydrated and markedly emaciated but only mildly acidotic. Chart VI begins with his admission. He was started on venoclysis and small amounts of oral feedings were begun on the second day. The clysis was discontinued

after three days, but the child refused most of his formula and vomited. After twenty-four hours the clysis was resumed for three more days while oral intake was gradually built up. He then showed steady improvement. All stool cultures were negative for pathogenic bacteria.

This represents a very smooth venoclysis in an emaciated child with caloric and protein intake adequate from the beginning. The only abnormal chemical finding was a decreased serum calcium after the diarrhea stopped.

Chart VI.

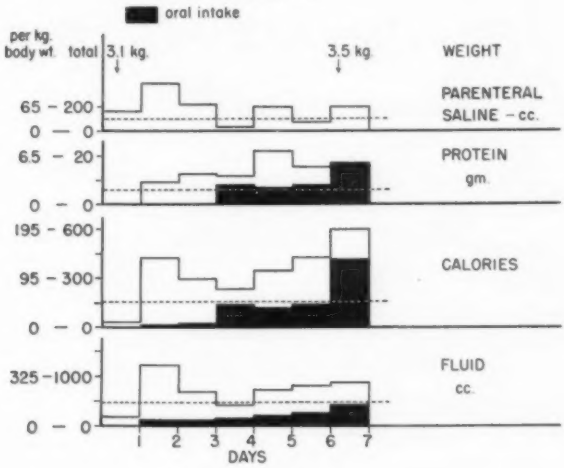
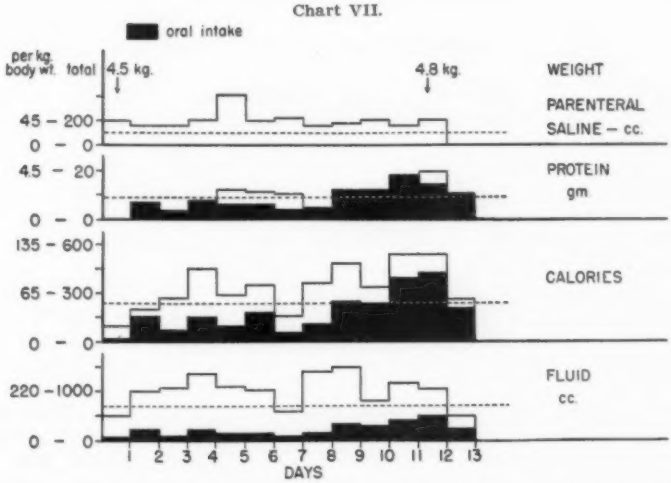



Chart VII.




CASE 6.—S. R., a 5-month-old infant admitted with a history of mild enteritis and vomiting, was treated with a short period of starvation and venoclysis and apparently recovered. One week later, fever, diarrhea, and vomiting recurred. Stool cultures were negative for pathogenic bacteria. Chart VII begins with the treatment of the relapse. She

was treated with venoclysis for thirteen days but oral feedings were never omitted. Her appetite was very poor for the first eight days and some vomiting occurred. Gradually the appetite improved but venoclysis was continued as the child still did not take sufficient food or fluid. She was never acidotic, but became hypocalcemic as the diarrhea ceased.

Chart VIII.

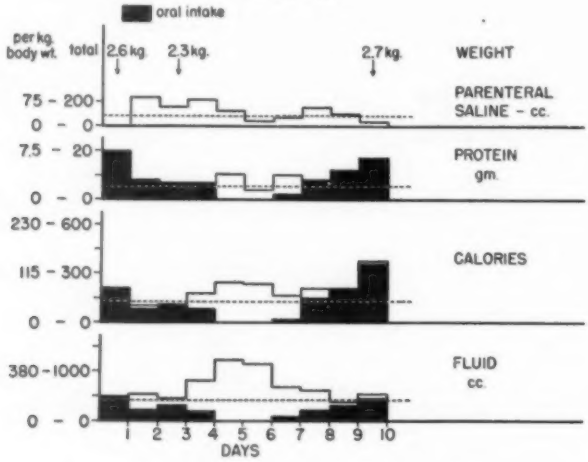
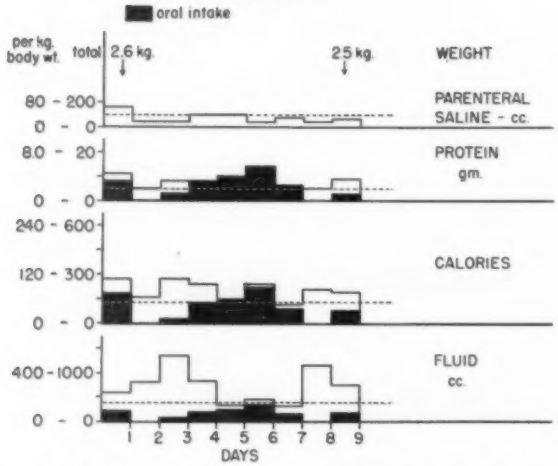



Chart IX.



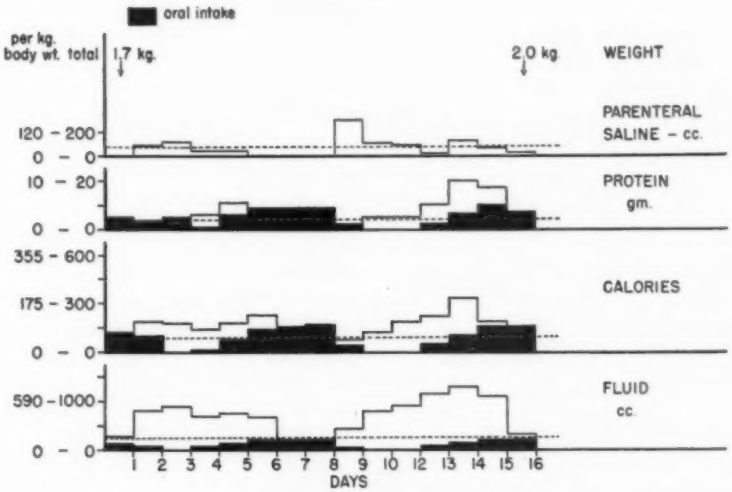

CASE 7.—D. G., a 7-week-old triplet who weighed 1.4 kg. at birth, had already had one or two bouts of diarrhea. He did well for two weeks after admission when diarrhea again developed. Stools were found positive for virus. Chart VIII starts at this point. Because of his small size, feedings supplemented by parenteral fluids were first tried. There was no abatement of the diarrhea, the child's appetite became worse, and vomiting occurred. He was starved for two days with all fluids given parenterally. Feedings were resumed and gradually increased while parenteral fluids were continued. Ten days after the commencement of parenteral fluid therapy he was doing well.

The serum chlorides were always high during his period of diarrhea with figures ranging from 127 to 135 milliequivalents per liter, and therefore little saline was given. The fluid intake exceeded 400 c.c. per kilogram in one twenty-four-hour period without any evidence of edema or other untoward results.

CASE 8.—D. G., a second one of the triplets, who weighed 1.7 kg. at birth, had a similar history. His stools were also positive for virus. Chart IX begins with his first period of parenteral therapy. He required two periods of intravenous administration of fluids, after which he did well on oral feedings with occasional supplements.

At the beginning of therapy serum chlorides were 128 milliequivalents per liter. They rose at one time to 143 milliequivalents per liter. Fluid intake reached as high as 500 c.c. per kilogram of body weight in one twenty-four-hour period without ill effects. This case also illustrates the low saline requirements of premature and young infants with diarrhea.

Chart X.




CASE 9.—B. A., an 11-day-old premature infant who weighed 1.7 kg. at birth, was admitted to the hospital weighing the same as at birth. She developed diarrhea six days later and lost 0.2 kg. in three days. Stools were positive for virus. Chart X begins at this point. Oral feedings were continued, supplemented with parenteral fluids, but the diarrhea continued, she refused to eat, and became acidotic. The acidosis was corrected with bicarbonate solution and saline, oral feedings were discontinued for two days, and continuous venoclysis was instituted. Feedings were then resumed, but after four days she began to refuse her formula, her diarrhea increased, and she was again found to be acidotic. Her acidosis and dehydration were corrected again, and she was taken off food for two days. Feedings were gradually resumed while parenteral fluid administration continued. Her appetite remained poor for some time, so that it was fifteen days after the commencement of therapy before she could go on oral feeding alone. Her weight had risen to 2 kg. She had a brief relapse a week or more later but was discharged well after two months weighing 2.8 kg.

Serum chlorides were also high and therefore saline intake had to be kept low. Fluid intake reached a peak of 700 c.c. per kilogram of body weight in one twenty-four-hour period.

Chart XI.

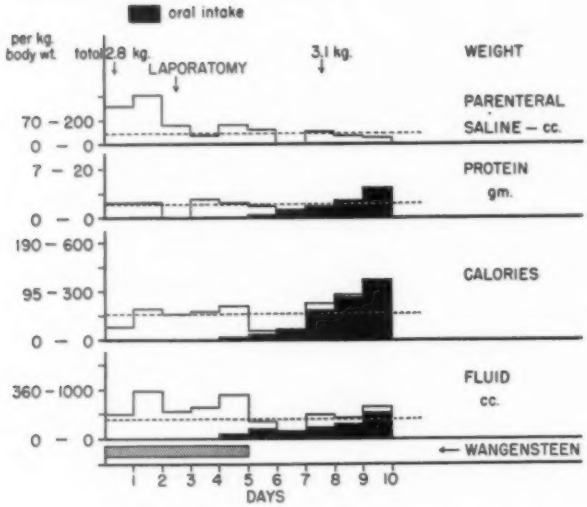
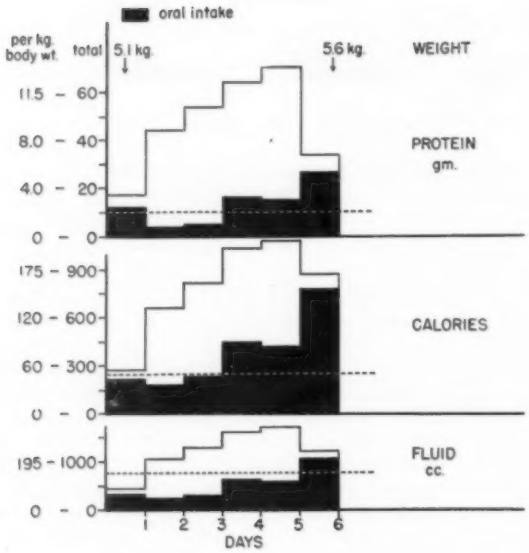



Chart XII.



The next two cases represent different indications for parenteral therapy.

CASE 10.—G. A., a newborn infant with a history of vomiting bile-stained material for six days, was admitted to the hospital. She had received saline subcutaneously several times. On admission she had obviously lost weight. Her blood chemistry was not significantly abnormal so that the main problem was one of parenteral alimentation. Chart XI portrays her course in the hospital. She was fed by venoclysis for two days and then a laparotomy was performed. Malrotation of the gut with volvulus was found. After operation she was fed exclusively by vein for two more days, then small amounts of glucose water and later increasing amounts of formula were given. At the end of ten days she had gained 0.3 kg. and looked well.

In the first few days considerable amounts of intestinal contents were aspirated by Wangensteen drainage but little fluid was lost following laparotomy.

CASE 11.—B. V., a one-year-old child with celiac disease, was admitted to the hospital weighing 5.5 kg. After a slight initial weight gain he had a rise in temperature and lost 0.7 kg. in the next two weeks. He became so weak that he was unable to ingest sufficient food or fluid to maintain his hydration or his weight. Chart XII begins at the point where he was started on continuous venoclysis of 5 per cent casein hydrolysate in 10 per cent glucose solution, and was offered at the same time a milk substitute by mouth. In six days he regained 0.5 kg., and his appetite became excellent so that he was able to maintain a steady weight gain on oral feedings thereafter.

This case illustrates the supplementation of oral intake by parenteral fluid, nitrogen, and calories in a child too weak to ingest and digest sufficient food by mouth.

## CONCLUSIONS

1. It has been shown that maintenance of fluid and electrolyte equilibrium by parenteral fluid administration is possible even in small infants during periods of partial or total withdrawal of oral feeding. With the use of glucose, whole blood, plasma, and casein hydrolysate, a gain in weight may be achieved.

2. A daily record of total intake of fluid, saline, calories, and nitrogen as part of a careful plan is an essential prerequisite of such a program.

3. Frequent observation of the clinical appearance of the infant and of his electrolyte and osmotic equilibrium is necessary.

4. Wide variation may be permitted in total fluid intake, provided salt intake is carefully regulated and is not excessive.

5. Premature and very young infants require less saline in proportion to their body weight than do older infants.

6. Contamination of the casein hydrolysate given, infection at the site of needle punctures, and thrombosis of the veins present a considerable problem. By the use of a closed system of administration, the more serious difficulties have been almost completely overcome. Thrombophlebitis and wound infection continue to be troublesome.

## REFERENCES

1. Elman, R.: Ann. Surg. **112**: 594, 1940.
2. Brunschwig, A., Clark, D. E., and Corbin, N.: Ann. Surg. **115**: 1091, 1942.
3. Clark, D. E., and Brunschwig, A.: Proc. Soc. Exper. Biol. & Med. **49**: 329, 1942.
4. Brunschwig, A., Bigelow, R. R., and Nichols, S.: J. A. M. A. **129**: 441, 1945.
5. Hartmann, A. F., Lawler, H. J., Meeker, C. S.: J. PEDIAT. **24**: 371, 1944.
6. Helfrick, F. W., and Abelson, N. M.: J. PEDIAT. **25**: 400, 1944.
7. Butler, A. M., and Talbot, N. B.: New England J. Med. **231**: 585, 1944.

# RETROLENTAL FIBROPLASIA

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Boston, Mass.

AN OCULAR maldevelopment characterized by the presence of some of the branches of the hyaloid artery and tunica vasculosa lentis has long been recognized. It had been called persistence of tunica vasculosa lentis or fibrovascular sheath, but these terms were misleading. It rarely occurred before extremely premature infants survived with any degree of frequency, and it sometimes involved only one eye in the full-term infant. Often the eye was needlessly removed following the erroneous diagnosis of retinoblastoma, a highly malignant tumor.

A research project to investigate this abnormality was motivated some six years ago by the examination of a patient with a bilateral ocular lesion. The history of extreme prematurity was outstanding. Search for other cases soon revealed that prematurity and the ocular abnormality, usually bilateral, were frequently associated. Since then, the study of this condition has become of major research interest in the Pathology Laboratory of the Massachusetts Eye and Ear Infirmary. From this study, several definite statements can be made.

The ocular lesion consists of:

1. A growth of embryonic connective tissue behind the crystalline lens.

2. The presence of only a few branches of the tunica vasculosa lentis carrying blood.

3. The presence of the hyaloid artery (seen in those cases where the retrolental mesenchyme does not cover the entire posterior surface of the lens).

4. An abnormally light-colored iris, usually blue, resulting from inadequate resolution of mesoderm on the anterior surface of the iris.

5. Retinal folds and even massive retinal separation which are found frequently enough, in instances where the fundus can be viewed in part, to be classed as a common primary finding.

6. Possible variations in severity from extensive involvement to minute traces which are commonly seen on the temporal side of the posterior lens surface.

7. Failure of the iris angle to differentiate.

8. Failure of any other part of the body to show abnormalities of a consistent type in association with the ocular abnormality, suggesting that the lesion is strictly a disturbance of the developing eye. One exception to this may be angiomas which are frequently in the skin. Reese[1] first recorded this. The fre-

Presented at the meeting of Region I, American Academy of Pediatrics, New York, N. Y., April 1, 1946.

Because of the illness of Dr. Terry, this paper was presented by Dr. Paul M. Runge, First Assistant Ophthalmic Surgeon, Massachusetts Memorial Hospital, and Clinical Assistant, Massachusetts Eye and Ear Infirmary, Boston, Mass.

quency of angiomas in our series is some 17 per cent, but their occurrence in premature infants without retrolental fibroplasia does not appear to have been recorded. The original opinion that mental retardation was an associated and not infrequent finding has been disproved by the observation of three children who had been diagnosed as feebleminded by experts. They have developed into individuals of unquestionably normal mentality under the guidance of preschool teachers skilled in working with the blind.

There are many changes which at the present time are considered to be sequelae or complications of the essential, abnormal, ocular development:

1. Lack or retardation in retinal development may be secondary when the abnormality is bilateral and a searching nystagmus is seen. Even when the lens is only partially covered, poor vision and macular differentiation are indicated by the searching nystagmus which is so frequently observed. The macula does not normally differentiate until some six months after full-term birth.

2. Early shallowing of the anterior chamber appears to be caused mechanically by contraction of the retrolental mesenchyme as it matures. Surgical removal of the lens restores the chamber. Later, the shallowing seems to result from a failure of aqueous humor to form in normal amounts.

3. Lentocorneal synechia often follow the obliteration of the anterior chamber.

4. Corneal opacities then develop in the region corresponding to the synechia.

5. There is failure of aqueous to form or to accumulate in normal amounts. Thus, the eye fails to grow.

6. Posterior synechiae and bound-down pupils develop.

7. Where some ability to form aqueous humor is retained, in perhaps 5 per cent of the cases, glaucoma occurs, but usually the eye coats are already strong enough to resist the stretching which would produce hydrophthalmos, a usual consequence of early and congenital or infantile glaucoma.

Any classifications such as Reese and Payne[1] have made, based on the severity of the involvement, should separate sequelae and complications from the essential features of the disease.

In the clinical study and the meager statistics available, the most striking association is that of retrolental fibroplasia with premature birth. Of the one hundred cases seen periodically, seventy-four are infants who weighed 3½ pounds or less at birth. Other observers seem to doubt that prematurity is even an exciting cause of the abnormality.[1, 2, 3] They appear to give no serious consideration to the fact that both Clifford[4] and I have seen this ocular abnormality develop in apparently normal eyes eight weeks or more after birth. We do not say that retrolental fibroplasia must invariably develop after birth, only that we have seen it develop in three cases. Again, the cause of prematurity varies in infants with retrolental fibroplasia, in similar proportions as the cause of prematurity in infants who do not develop the abnormality.

Thus, there is no common ground for the production of prematurity and production of the eye defect. Their relationship, however, is so frequent that it must be explained.

Recently, Bakwin,[5] in discussing a paper by Sitchevska analyzing all cases available from the literature, stressed the ratio of males to females as eight to five. If the ratio is maintained, could it mean that absence of ovarian hormones, even those from the premature female ovary, is a stimulating factor, or perhaps that the presence of male sex hormones, even from the premature testicles, favors retrolental fibroplasia formation? Of course, such a question is an exercise in considering and weighing all conceivable etiologic factors. Although we think of such questions, and may even give expression to them, we do so with considerable mental reservation.

Bakwin also points out the apparent lack of parallelism in frequency of retrolental fibroplasia and the increasing survival rate of the premature infant. This is, indeed, worthy of further consideration. All of us will agree that we do not have a sufficient number of cases for us to feel sure that our present statistics are of proved value. I am still puzzled over the apparent variations in the frequency of retrolental fibroplasia in different medical centers. Proof that there is a variation is lacking, but there are strong suggestions that such a variation does exist. Some individual differences in technique of premature infant care in these centers may act as at least an exciting etiologic factor.

None of the various classes of etiologies can be absolutely excluded. These include heredity, those causes operating before birth, those arising through premature separation from maternal hormones, the precocious functioning of systems such as the respiratory, digestive, and cardiovascular, the heat regulatory center, and those arising through precocious exposure to light. It appears that a common exciting factor is related to premature birth and incubator life. It seems logical that, of the etiologies limited to the eyes alone, precocious exposure to light is still the leading factor in the cause of ocular developmental abnormalities, yet no clinical or experimental finding strongly supports this. Heredity seems least likely. To know whether we are studying one disease entity or several which have similar clinical features but different causes would more clearly define our problem.

The value of treatment from the ophthalmologist is relatively meager. We have no cure. We do have medical and surgical treatments aimed at prevention or eradication of complications.

The greatest value, however, is to be derived from social service workers and preschool teachers. The social service worker first helps the parents to overcome their emotional sense of guilt and frustration and then provides suggestions and resources available to make a good citizen of the blind child. The preschool teacher for the blind aids the parents in teaching their child to chew solid food, to dress himself, and then to appreciate the nature of the world about him.

This ocular abnormality is still one of the great challenges in relation to prematurity. The prognosis at best is questionable, but until it is proved to be

hopeless, we have no right to abandon all efforts at treatment. To have a really close relationship between the pediatrician and the ophthalmologist, not only in routine clinical studies, but also in experimental and investigative research, would speed the solution in a mutually advantageous manner.

## REFERENCES

1. Reese, A. B., and Payne, F.: Persistence and Hyperplasia of the Primary Vitreous (Tunica Vasculosa Lentis or Retrolental Fibroplasia), Am. J. Ophth. 29: 1, 1946.
2. Krause, Arlington C.: Congenital Encephalo-ophthalmic Dysplasia of Unknown Etiology, Arch. Ophth. In press.
3. Mann, Ida C.: Personal communication. Discussion of Reese and Payne paper.[1]
4. Clifford, S.: Personal communication.
5. Bakwin, R.: Retrolental Fibroplasia: Discussion of Dr. Olga Sitchevska's Paper, Presented at the Ophthalmological Section of the Academy of Medicine, New York, N. Y., Feb. 18, 1946.

# MUCOUS CYST AT BASE OF TONGUE AS A CAUSE OF SUDDEN DEATH IN AN INFANT

## Report of a Case

La Mont Whittier, M.D., and Edward F. Dombrowsky, M.D.
Ancon, Canal Zone

ALTHOUGH mucous cysts of the lips, cheeks, and lower surface of the tongue are not uncommon, the literature contains relatively few reports of such cysts located at the base of the tongue. Because of the presence of numerous glands in this area, as well as the complex embryological development of the tongue, one would expect to see such lesions more frequently. Cysts at the base of the tongue may originate either from incomplete obliteration of the lingual portion of the thyroglossal duct, or from mucous glands. The former are usually found in the midline beneath the foramen caecum.[1] They are lined by stratified squamous or ciliated epithelium. Mucous or retention cysts occur when the mucous glands in this area become obstructed. Such cysts are usually located between the epiglottis and the foramen caecum, and may be either in the midline or lateral to it.[1] Reimann[2] suggests that mucous cysts in this area may originate from the efferent tubules which accompany the thyroglossal duct.

Thyroglossal cysts are rarely present at birth, but generally form between the third week and the thirty-first year of life.[3] Mucous retention cysts at the base of the tongue have been described most often in infants. In this location they may become large enough to produce laryngeal stridor and asphyxia.[1]

The purpose of presenting this case is not to point out a rare lesion but rather to emphasize that a large mucous cyst at the base of the tongue can cause asphyxia and death.

### CASE REPORT

A 2-month-old Panamanian mestizo male was admitted because of difficulty in breathing. The parents stated that the baby had appeared to breathe with more or less difficulty ever since he came home from the hospital after a normal delivery. The respiratory difficulty had become worse previous to admission. Physical examination revealed a well-nourished and hydrated male infant with mild inspiratory difficulty and with evidence of a mild upper respiratory infection. The temperature was 99.2° F. Laboratory procedures, including blood calcium and phosphorus, and x-ray of the chest, revealed nothing abnormal.

Mild inspiratory stridor was noted only at times when the baby was lying on his back. This would disappear when the baby was turned onto his abdomen. He took his feedings well with no vomiting. He was discharged with the diagnoses of rhinopharyngitis, acute catarrhal otitis media, and congenital laryngeal stridor.

Eight days later the baby was readmitted to the hospital with the complaints of refusal to eat and of coughing, choking, and vomiting when the formula was forced. He was dehydrated and had lost one pound in the interval between admissions. The temperature was 100.8° F. There were musical râles over the left lung. Findings from routine laboratory examinations were within normal limits.

From the Pediatric Service and The Board of Health Laboratory, Gorgas Hospital.

The baby took his feedings with reluctance, often choking and sometimes vomiting when they were forced. He also vomited frequently following feedings. Transient cyanosis often appeared when he choked or vomited. Because of the vomiting, repeated clyses were necessary to maintain hydration. Three days after admission, the infant had been given his formula with considerable difficulty and had several spells of transient cyanosis. Shortly after this feeding he was found to be extremely cyanosed. Breathing had stopped. Vomitus was noted about the mouth and neck. The heart was beating feebly but soon ceased despite artificial respiration and stimulants. Esophageal-tracheal fistula, achalasia of the esophagus or possibly some form of congenital laryngeal stridor were among the diagnoses entertained prior to death.

*Gross Autopsy Observations.*—A complete autopsy was performed three and one-half hours after death. No abnormalities were noted in any structures other than the tongue.

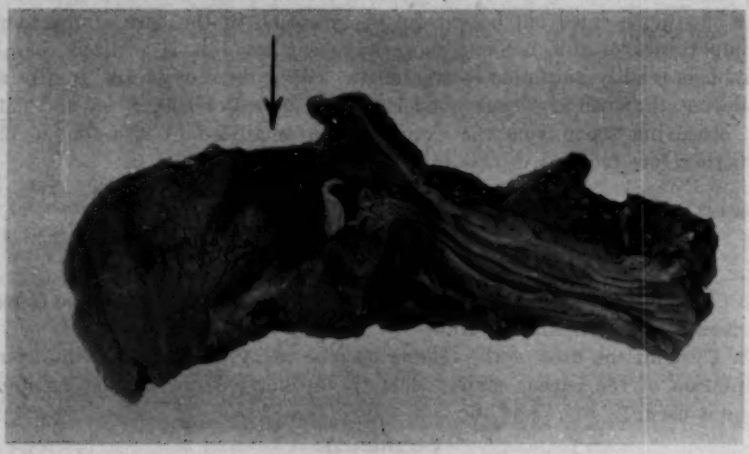

Fig. 1.—In the photograph the arching dome of the cyst appears depressed, but this is probably due to postmortem discoloration. However, the size and position in relation to the epiglottis are illustrated nicely. Note the raphe connecting the cyst to the epiglottis.

*Tongue:* At the base of the tongue and slightly to the right of the midline, a bluish-gray, thin walled cyst was observed. This cyst was circular, protruded 1.5 cm. from the superior surface of the tongue, extended 1.0 cm. into the substance of the tongue, and measured 2.5 cm. in diameter. The posterior margin of the cyst was located 0.2 cm. anterior to the base of the epiglottis and was attached to it by a thin membranous raphe. Lifting the tongue or pushing it slightly posteriorly caused the cyst to press against the epiglottis, completely closing the laryngeal orifice. This obviously was the mechanism which caused asphyxia and death in this patient. The cyst was filled with a thick, clear, mucoid material. The lining of the cyst was smooth and pale gray.

*Microscopic Examination.*—The dome of the cyst wall consisted of three distinct layers. The outermost zone was composed of a narrow layer of atrophic surface squamous epithelium. The central and thickest layer consisted mainly of compressed muscle fibers and a few scattered zones of flattened mucous glands. The lining of the cyst wall was composed of a layer of cuboidal to low columnar cells varying from one to two cells in thickness. Sections stained with mucicarmine revealed the glands within the muscular layer and the cells lining the cyst to be mucous in type. The cyst contents showed similar staining characteristics.

## DISCUSSION

As stated by Holt and McIntosh,[4] "sudden death is not a very uncommon occurrence in infants who are apparently healthy or appear to be suffering

only from some minor ailment." Asphyxia is among the more frequent of the conditions listed as possible causes of sudden death. This may result from the aspiration of food, mucous, or foreign bodies. Abramson[5] gives prominence to accidental mechanical suffocation as a cause of death in infants. Woolley[6] questions the frequency with which the diagnosis of suffocation due to bedding, sleeping attire, or other mechanical means is made. He believes that careful autopsies in all such cases would often reveal other causes such as overwhelming infections and congenital anomalies.

Although uncommon, a mucous retention cyst at the base of the tongue should also be considered in the differential diagnosis of asphyxia. Whenever unexplained choking, dyspnea, or cyanosis occurs in an infant, a cyst of this nature should be ruled out by careful visualization of the base of the tongue. The importance of this becomes more apparent when it is realized that this condition is readily amenable to treatment. Since these cysts are usually near the midline, the ordinary large wooden tongue depressor may cover and flatten them, obscuring them from the examiner. A small infant size tongue blade should therefore be used in this examination.

## SUMMARY

1. A case of sudden death due to a mucous retention cyst at the base of the tongue is reported.

2. Though uncommon, cysts in this area must be considered in the differential diagnosis of asphyxia in infants.

3. Cysts at the base of the tongue may be easily overlooked in the routine examination of the buccal cavity when the ordinary large wooden tongue depressor is used.

## REFERENCES

1. Duncan, G. W., and Danile, R. A., Jr.: Cystic Tumor of the Tongue: Report of an Unusual Case, Arch. Surg. 44: 164, 1942.
2. Reimann, S. P.: Pathology for Students and Practitioners, ed. 8, Philadelphia, 1929, P. B. Blakiston's Son and Co., vol. 1, p. 507.
3. Thoma, K. H.: Oral Pathology, ed. 1, St. Louis, 1941, The C. V. Mosby Company, p. 273.
4. Holt, L. E., Jr., and McIntosh, R.: Diseases of Infancy and Childhood, ed. 2, New York, 1940, D. Appleton-Century Co., p. 60.
5. Abramson, J.: Accidental Mechanical Suffocation in Infants, J. PEDIAT. 25: 404, 1944.
6. Woolley, P. V., Jr.: Mechanical Suffocation During Infancy, J. PEDIAT. 26: 572, 1945.

# The Academy Study of Child Health Services

## REPORT OF THE COMMITTEE FOR THE STUDY OF CHILD HEALTH SERVICES

Less than one year ago, when the Committee for the Study of Child Health Services made its annual report in Detroit, this Academy study was just getting under way. The organization had been planned, a pilot study had been done, and financial support solicited. At that time, however, assets were measured in terms of optimism rather than cold reality. The Academy had committed itself to a nationwide study of child health services, but the members had little appreciation of the magnitude of the task or the fact that every individual member had a job to do if the project were to be successful. Today, ten months later, the Academy is well along the road toward a goal that increases in significance as it is approached.

### STATE STUDIES

First, a glance at the state programs: This is the most remarkable phase of our progress, and the credit is due to state chairmen together with their executive secretaries and advisory committees appointed for the purpose. Less than a year ago they were confronted by difficulties which appeared insurmountable. Today these difficulties have been met. The Study has been launched in all but two states in the country, including the District of Columbia and the Territory of Hawaii. The remaining two states are expected to start soon. In four states and the District of Columbia, the collection of data is complete, or nearly so, and the schedules sent in to the central office for analysis and tabulation. It is expected that all states will complete this phase of the study during the next few months. Despite earlier misgivings as to finding suitably qualified, full-time executive secretaries to assist state chairmen, they appeared when the importance of the Academy's venture began to be appreciated. A total of fifty-seven full-time, paid, executive secretaries have been engaged in the study throughout the country; of these, twenty-nine are pediatricians, the remainder coming from a variety of medical and sociological backgrounds. A year ago the office of State Chairman had no treasury or financial responsibility. However, state chairmen have financed their state programs to a collective total of approximately $450,000.

### REPORTING THE STUDY

At the outset it was assumed by the Committee for the Study of Child Health Services and its director that their duties would be fulfilled in recording the factual data in one, overall report for the country as a whole. It now appears that this is only a part of the job. Recently, as the interest of local groups has grown, state chairmen have repeatedly requested the Executive Staff to return to them statistical data in sufficient detail to serve as a basis for reports for their own states. Consequently, in reporting the Study, the emphasis shifted from the national level to state, county, and local levels. This is a thoroughly wholesome development and has been willingly accepted by the Executive Staff despite the fact that it has increased the work far beyond that which was originally anticipated.

In planning the statistical tabulations for the state reports, it became apparent that there was an urgent need for members of the Executive Staff to meet with state chairmen in order to provide opportunity for a free interchange of opinions and to define in specific terms the amount and type of material to be returned to the states. For this purpose, three regional meetings were held during September in Chicago, San Francisco, and Washington. These meetings have been described in some detail in recent issues of THE JOURNAL. They were all

To have been presented at the annual meeting in Pittsburgh in November, 1946, which was cancelled.

well attended, clarified many problems, and gave significant impetus to the preparation of state reports. During the last of these three regional conferences held in Washington September 30 and October 1, there was a meeting of the committee, at which the discussion was chiefly concerned with establishing methods to assure that the information gathered during the study would be adequately and promptly reported at the state level as well as the national level. As a result of this discussion, the committee wishes to present to the Executive Board certain recommendations. At the state level these recommendations are intended to provide state chairmen a suitable opportunity to report the information before it is released to anyone else. At the national level the committee considers that its assignment will have been fulfilled when the data are duly recorded in a factual report, a report which should stop with a presentation of facts and should not attempt to make recommendations arising from those facts. *But* the committee is naturally anxious that this study into which has been poured so much time, effort, and money, should be put to proper use. Therefore, a further recommendation deals with the formation of a committee charged with the responsibility of implementing the study and translating it into an action program to accomplish the Academy's goal of improved health services for children.

### STATISTICAL ANALYSIS

The preparation of detailed and tabulated material for forty-eight states, the District of Columbia and the Territory of Hawaii means a volume of work far beyond that which was originally planned. The statistical analysis that is now under way is such that it would take one man 100 years to complete. The Study Staff has been told to complete it by the end of next year, fourteen months from present date. Rather than having one poor soul growing old in the cause, a statistical team of fifty or maybe more is being developed to finish the job in the allotted time. The Academy is fortunate in having secured the services of Mr. Rollo Britten to act as chief of this statistical team. Having retired from the U. S. Public Health Service, he is now employed on a full-time basis by the Academy.

### CENTRAL OFFICE

A year ago the central office of the study was in a small room of about seventy square feet made available through the kindness of Dr. Wall and the Children's Hospital in Washington. This room was barely large enough to accommodate the director and half a secretary; the other half sat in the hall. In February, 1946, when the Study was really under way, the office had to expand but there were insufficient funds for office rent. Therefore, the Director accepted a generous offer from the Surgeon General to occupy offices without charge in the Bethesda buildings of the U. S. Public Health Service. The staff is still in these offices, but again more space is needed to accommodate the large statistical force described above. In contrast to the seventy square feet of a year ago, some 6,000 to 8,000 square feet are now needed. It is not only more appropriate but indeed necessary to establish the office in downtown Washington, but it has been almost impossible to find suitable space for a short-term lease at a figure less than astronomical. Recently, with the approval of the Committee Chairman, the director requested and received from the President of the Academy, authority to sign a lease for rental of property at 2346 Massachusetts Avenue, NW, where, being a residential district, the rate for office space is about half that of the downtown area. Permission to establish an office at this location is now awaiting action by the Board of Zoning Adjustment of the District of Columbia. It would be appropriate for the Executive Board to confirm the authority given by the President to the Director to sign this lease or, failing favorable action from the zoning board, to sign a lease for other property at rates within the budget allowance.

### STUDY OF PEDIATRIC EDUCATION

During the coming winter, as the collection of information from the states is completed, the Study of Pediatric Education, the second major part of the Academy Study will be developed. For this purpose a subcommittee has been formed consisting of Dr. James L. Wilson, Chairman, and six additional professors of pediatrics as follows: Drs. Henry Poncher, Samuel Levine, Waldo Nelson, Robert Lawson, Ralph Platou, and Francis Scott Smyth. Each has agreed to direct and participate in the Study in approximately ten medical schools in his

section of the country, thus covering all sixty-eight schools in the United States. The schools for which each is responsible were listed in the October issue of THE JOURNAL. A preliminary meeting of this committee was held in Washington, D. C., in June of this year at which time the first draft of the questionnaire schedules for this portion of the study (Series IV) and the general plan of action were discussed. Dr. John Mitchell, who, up to November 1, was director of the state program for Pennsylvania, is now director of this phase of the study. He, together with Dr. Hubbard, worked out a tentative schedule allowing one month to visit the medical schools in each of the seven areas during the current academic year. At the beginning of the month's visit to each area, the committee member responsible for that area will call a meeting of the chiefs of the pediatric departments of the schools assigned to him. Then, insofar as circumstances allow, the committee member will visit each school together with Dr. Mitchell or Dr. Hubbard. In this way the study of each school should include the opinions of an outstanding teacher of pediatrics plus those of a member of the Executive Staff whose past experience includes both teaching and practice and whose function will be to assure that in each school the same techniques of gathering information are used. Thus a consistent and most interesting picture of pediatric education should be obtained.

### FINANCIAL REPORT

Finally a report on the financial status. On Jan. 25, 1946, Dr. Grulee turned over to the Director of the Study $11,525.84. That's all there was except hope. Today the budget exceeds $1,000,000. As mentioned above, nearly half of this is the collective total cost of state programs which has been met, not without considerable difficulty by state chairmen from sources within their own states including county chapters of the National Foundation for Infantile Paralysis, state health departments, medical and pediatric societies, contributions of individual pediatricians, local grants, and other local sources.

The finances of the Central Office of the Study are being administered by the Director through three separate accounts.

1. The first account designated as the "Foundation Account" was set up to administer a two-year grant of $116,000 from the National Foundation for Infantile Paralysis. On April 5, 1946, $67,500 was received in accordance with the budget submitted for the first year. The balance, $48,500, is due April 1, 1947.

2. The second account, designated as the "National Institute of Health Account," was opened in November to administer a grant to the Academy from the National Institute of Health of the U. S. Public Health Service. This grant is intended to cover the cost of statistical analysis from Oct. 1, 1946, including salaries, office rent, machine rental, office equipment, and supplies for the statistical division. It will be recalled that in the early planning of the study, the committee requested the cooperation of the U. S. Public Health Service and the U. S. Children's Bureau. Both government agencies responded wholeheartedly; the Surgeon General offered to support the Academy in the technical and statistical aspects of the study in which the Academy had neither the necessary experience, personnel, nor equipment. As of recent date when it was possible to estimate the amount of work to be done by the statistical division, the director in the name of the Academy submitted to the Surgeon General a request for a grant-in-aid from the National Institute of Health based on a budget of $249,750 to meet the further expenses of this division. As shown in the attached statement this request was made for the period Oct. 1, 1946, to Dec. 31, 1947, broken into two parts: $128,550 for nine months from Oct. 1, 1946, to June 30, 1947, and $121,200 for six months from July 1, 1947, to Dec. 31, 1947. The latter amount was considered subject to revision in the light of experience gained by next summer. After due consideration by the National Advisory Health Council the amount requested for the first term was approved in full, with assurance given that further support would be forthcoming to complete the study.

3. The third account which actually was the first one opened is designated as the "Academy Account." Into this account have been placed receipts from all other sources, including the reserve fund of the Academy itself, a grant from the Field Foundation, the New England Pediatric Society, and contributions from pharmaceutical and commercial houses. These receipts together with the expenditures from this account are also shown in the attached statement.

If to the receipts in these three accounts is added the total of estimated state budgets and an estimate of the value of services rendered by the U. S. Public Health Service and the U. S. Children's Bureau, a grand total somewhat in excess of $1,000,000 is shown as the anticipated cost of the Study of Child Health Services.

### THE NEXT STEP

The Academy may look with justifiable pride at having planned, organized, and successfully brought to the halfway mark a nationwide study of child health services. It may look with pride, not unmixed with awe, at having been able to call forth over $1,000,000 to finance this study. It may look with pride at the publicity which its declared objectives have received throughout the country in professional journals and the lay press. However, this committee wishes to express its realization that success breeds responsibility and that unless the Academy makes full use of the interest which it has aroused and the information which it has collected, it will be blamed for a dismal failure. There is no thought that the Academy will fail, but it is felt that more attention must be given *now* to the next step. How are the results of this fact-finding study to be translated into an action program? What sort of a committee should draw up and implement recommendations arising from the facts? How, in short, is the Academy going to move closer toward its goal of planning for better and more evenly distributed health services for children? These questions should be a major concern of the Academy at this meeting.

Respectfully submitted,

JOHN P. HUBBARD, Director
WARREN R. SISSON, Chairman
ALLAN M. BUTLER
HARVEY F. GARRISON
HENRY F. HELMHOLZ
LEE FORREST HILL
JOSEPH I. LINDE
ARTHUR H. LONDON, JR.
JOSEPH S. WALL
JAMES L. WILSON

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### CERTIFICATE OF THE AUDITOR

November 6, 1946

To the Executive Board
American Academy of Pediatrics
Evanston, Illinois
Gentlemen:

I have made an examination of the financial accounts and records of the American Academy of Pediatrics, Study of Child Health Services for the period from the opening of the accounts in February, 1946, to Oct. 31, 1946.

Without making a detailed audit of all transactions, I have satisfied myself that all recorded cash receipts were deposited in banks, and I examined cancelled checks and vouchers for the greater part of the disbursements. The bank balances have been verified by certificates from the bank. Accounting records and other supporting evidence have been examined by methods and to the extent I deemed appropriate.

In my opinion the accompanying statements of receipts and disbursements and reconciliation of accounts present fairly the financial conditions of the Study of Child Health Services at Oct. 31, 1946, and the results of its operations for the period under review, in conformity with generally accepted accounting principles.

Very truly yours,
MAX R. BYERS
Certified Public Accountant

Washington, D. C.

STATEMENT OF RECEIPTS AND DISBURSEMENTS, FEB. 1, 1946, TO OCT. 31, 1946

| | | |
|---|---|---|
| *Receipts:* | | |
| Restricted contributions: | | |
| National Foundation of Infantile Paralysis | $67,500.00 | |
| Unrestricted contributions: | | |
| American Academy of Pediatrics | 16,022.16 | |
| Mead Johnson & Company | 15,503.68 | |
| M & R Dietetic Laboratories Incorporated | 10,000.00 | |
| Carnation Company | 10,000.00 | |
| Pet Milk Company | 10,000.00 | |
| New England Pediatric Society | 500.00 | |
| Lederle Laboratories | 5,000.00 | |
| Field Foundation | 5,000.00 | |
| Cutter Laboratories | 500.00 | |
| *Total Receipts* | | $140,025.84 |
| *Disbursements:* | | |
| Salaries (17 persons) | $37,460.36 | |
| Travel | 9,966.60* | |
| Office equipment | 2,865.48 | |
| Postage | 1,962.78 | |
| Office supplies | 1,716.70 | |
| Printing and publicity | 6,983.30 | |
| Miscellaneous | 50.65 | |
| Telephone and telegraph | 987.72 | |
| State programs | 16,870.02 | |
| Periodicals and books | 35.15 | |
| Social security taxes | 53.84† | |
| Car purchase, upkeep, and travel by car | 2,643.81 | |
| Premium on bonds | 187.50 | |
| Addressing and mailing | 1,203.25 | |
| Educational study | 806.93 | |
| *Total Disbursements* | | 83,794.09 |
| *Balance:* | | $ 56,231.75 |

*Exhibit "A"*

STATEMENT SHOWING RECONCILIATION OF ACCOUNTS, OCT. 31, 1946

| | |
|---|---|
| Cash in bank—Foundation account | $ 25,160.10 |
| Cash in bank—Academy account | 31,896.20 |
| *Total Cash in Bank* | $ 57,056.30 |
| Balance available for expenditure, Exhibit A | $ 56,231.75 |
| Income taxes withheld from salaries | 764.30 |
| Social Security taxes deducted from salaries | 60.25† |
| *Total* | $ 57,056.30 |

*Exhibit "B"*

COMMENTS

Receipts from the National Foundation for Infantile Paralysis are maintained in a separate bank account designated as the "Foundation Account." Disbursement of these funds is restricted within certain budget limitations. Separate accounting records are kept for receipts and disbursements from this "Foundation Account." The unrestricted funds are deposited in what has been designated as the "Academy Account." A proper record of these receipts and their disbursement is maintained. For the purpose of the accompanying statements the accounts have been consolidated.

*Includes travel expense for regional meetings and for committee and field staff.
†Subject to refund pending legislative ruling.

From the following source of funds received by the American Academy of Pediatrics during 1945 and 1946:

| | | |
|---|---|---|
| American Academy of Pediatrics Reserve Fund | | $18,000.00 |
| Mead Johnson & Company | $18,000.00 | |
| the following amounts were expended for preliminary study from March, 1945, to February, 1946 | 2,496.32 | 1,977.84 |
| | $15,503.68 | $16,022.16 |

In order to cover further expenses of the statistical division application was made on Aug. 7, 1946, for a grant of $128,550 from the National Institute of Health of the U. S. Public Health Service for the period Oct. 1, 1946, to June 30, 1947, with an additional $121,200 for the period July 1, 1947, to Dec. 31, 1947; the latter amount being subject to revision in light of experience gained by July 1, 1947. This grant has been approved and a check in the amount of $128,550 was received Nov. 1, 1946, expenditures from which may be retroactive to Oct. 1, 1946.

Following is a list of funds pledged to the American Academy of Pediatrics, Study of Child Health Services for receipt in 1947:

| | |
|---|---|
| National Foundation for Infantile Paralysis | $48,500 |
| Field Foundation | 5,000 |
| Mead Johnson & Company | 10,000 |
| M & R Dietetic Laboratories, Inc. | 10,000 |
| Pet Milk Company | 10,000 |
| Carnation Company | 10,000 |
| Total pledged for 1947 | $93,500 |

Figures were not available at this time for the value of services rendered from July 31, 1946, to Oct. 31, 1946, by the U. S. Public Health Service and the U. S. Children's Bureau, but the following were set forth at a previous writing as of July 31, 1946:

Value of services rendered from July 1, 1945, to July 31, 1946, by:

| | |
|---|---|
| U. S. Public Health Service | $26,587 |
| U. S. Children's Bureau | 10,260 |
| Total | $36,847 |

Value of *anticipated* services rendered from Aug. 1, 1946, through Dec. 31, 1947:

| | |
|---|---|
| U. S. Public Health Service | $47,600 |
| U. S. Children's Bureau | 17,000 |
| Total | $64,600 |

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**Addendum**

In the report on the Academy Study of Child Health Services last month, The Albany Medical College, Albany, N. Y., and University of Vermont College of Medicine, Burlington, Vermont, which were assigned to Dr. Samuel Z. Levine, were inadvertently omitted.

# The Social Aspects of Medicine

## COMMUNICATION

### SUMMARY REPORT OF MEETING OF MATERNAL AND CHILD HEALTH ADVISORY COMMITTEE AND CRIPPLED CHILDREN ADVISORY COMMITTEE. U. S. CHILDREN'S BUREAU, WASHINGTON, D. C. SEPTEMBER 16 and 17, 1946

On Aug. 10, 1946, Congress passed legislation amending Title V of the Federal Social Security Act, increasing the amounts authorized for annual appropriation to be used as grant-in-aid to the States as follows:

A. Funds for Maternal and Child Health Services increased from $5,820,000 to $11,000,000.

B. Funds for Crippled Children's Services increased from $3,870,000 to $7,500,000.

C. Funds for Child Welfare Services increased from $1,510,000 to $3,500,000.

The Children's Bureau called the meeting of the Maternal and Child Health and Crippled Children Advisory Committees on September 16 and 17 at Washington, D. C., to confer upon matters relating to the extension and improvement of health services for mothers and children.

Dr. Oscar Miller, orthopedic surgeon, Charlotte, North Carolina, and Dr. Nicholson Eastman, Professor of Obstetrics, Johns Hopkins University, Baltimore, Maryland, served as co-chairmen of the Committees. Sixty-three of the seventy members of the Maternal and Child Health and Crippled Children Advisory Committees attended the meeting. Thirteen, invited guests from the fields of medicine, dentistry, nursing, and medical social work also attended.

This was the first meeting of the Advisory Committees held since the transfer of the Children's Bureau from the United States Department of Labor to the Federal Security Agency. Mr. Watson B. Miller, Federal Security Administrator, greeted the members of the Advisory Committees and guests at the opening session, and expressed his deep interest and concern in the development of improved health services for mothers and children in all sections of the United States. Mr. Miller stated that he had been acquainted with the work of the Children's Bureau over a period of years and believed that there should continue to be such a unit in the Federal Government which concerns itself solely with the health and welfare of mothers and children, and that he had no intention of dismembering the Bureau and scattering it among the other offices within the Federal Security Agency. He indicated, however, that many mutual benefits would be derived by having the Children's Bureau as an integral part of the Federal Security Agency working in close association with the numerous other units concerned with the fields of health, welfare, and education.

Mr. Arthur J. Altmeyer, Commissioner for Social Security, Federal Security Agency, spoke briefly before the conference and explained the position of the Children's Bureau in the Social Security Administration. He commented upon the social philosophy underlying the Social Security program and referred to the important role played by the Children's Bureau in the development of health and welfare services for mothers and children. Mr. Altmeyer reaffirmed the position taken by Mr. Miller in maintaining the integrity of the Children's Bureau, and indicated that full support would be given the Bureau in carrying forward the program for continued extension and improvement in health services for mothers and children.

During the two-day meeting, members were divided into seven subcommittees to consider special subjects and make such recommendations to the full committees as were indicated. The following abstract of the more than sixty recommendations adopted by the

committees has been prepared for the interest of the pediatricians (copies of the full report of the joint meeting of the two Advisory Committees will be available in the near future):

*Training of Personnel.*—In the deliberations of each subcommittee and in the discussions by the full committees it was quite apparent that there was a unanimity of opinion as to the urgent need for the training of professional personnel as a first step in the development of new programs or in the extension of existing programs. Emphasis was given to the use of regularly established and approved educational institutions for providing such professional training. It was urged that funds be made available to strengthen the essential training programs in recognized educational institutions, and that a closer working relationship be developed between the official agencies administering maternal and child health and crippled children's services, and the educational institutions. Several suggestions were made as a working basis for such cooperative relationships, with the added comment that the arrangements should be such as to safeguard the freedom of the educational institution on the one hand and the administrative responsibility of the State agency on the other. It was also recommended that the State agencies administering maternal and child health and crippled children's services take appropriate steps to encourage and assist the various professional schools in the preparation of professional personnel with reference to the social aspects of health and medical services and for participation in community health services. Special mention was made of the need for training administrative personnel in the health field in order to relieve medical and technical specialists from procedural matters. The committees pointed to the responsibility of the Children's Bureau in exploring training needs and for assisting educational institutions and State agencies in developing cooperative relationships affecting the training of personnel.

*Extension and Improvement of State Services for Crippled Children.*—The advisory committees reaffirmed the recommendations made to the Children's Bureau in December, 1944, calling for expansion of the State services for crippled children. The committees called attention to the special needs of children with rheumatic fever, cerebral palsy, orthodontic defects, speech and hearing defects, epilepsy, and chronic illnesses, but made no recommendation with respect to priority in the development of such services. However, it was recommended in the extension of the State programs to include new services, that these should be developed in a limited area, providing the full range of preventive, diagnostic, and technical services, rather than in a piece-meal manner. Considerable emphasis was given to the importance of safeguarding the quality of care being provided crippled children by maintaining qualification standards for the selection of professional personnel to render services for crippled children and by the State agency conducting periodic impartial reviews of the quality of professional services through the use of committees of qualified specialists. It was also urged that the Children's Bureau undertake evaluation studies of the special programs to determine their effectiveness. The committees recommended that the Children's Bureau conduct a national fact-finding survey to determine the incidence and prevalence of cerebral palsy and other factors affecting the care and treatment of such children. Attention was called to the need for the development of centers in conjunction with approved medical schools for the training of personnel in the care and management of the cerebral palsied child, and a recommendation was adopted that the Children's Bureau use its resources in developing appropriate plans for such training facilities.

*Development of New and Improvement of Existing Services for the Care of Maternity Patients.*—The committees reviewed current problems related to maternity care and recommended that State health departments assist hospitals in establishing blood banks in strategic areas, especially for the benefit of maternity patients. It was also recommended that as hospitals increase their facilities under the hospital construction program, major attention be given to the need for additional hospital maternity facilities. It was suggested that consideration be given also to the advisability of providing annexes for antepartum and postpartum care for patients not requiring full professional care at the hospital. It was the opinion of the committees that every State health department should assure that adequate provisions exist for medical, nursing, medical social and nutrition advisory services to hospitals with maternity services.

It was pointed out that maternity care services and tuberculosis control programs should cooperate in assuring every maternity patient a routine chest x-ray early in pregnancy as a part of her complete prenatal examination.

The Committees urged that State health departments, in cooperation with teaching centers whenever possible, develop obstetric clinical consultation services to general practitioners especially for those residing in rural areas. The committees believed that there should be developed in at least one needy rural area in the United States in cooperation with a medical teaching institution a comprehensive maternity care project. Such a project as visualized by the Committees would assure the highest quality of medical, nursing, nutrition and medical-social services and hospital care, and would be of inestimable value in determining how maternity care of high quality can best be provided in such areas.

The committees recommended that the Children's Bureau prepare and issue for the public a small leaflet outlining the essentials of adequate maternity care and that appropriate steps be taken to assure the widest possible distribution.

*Development and Improvement of Facilities and Services for the Care of the Newborn Infant With Special Reference to Those Prematurely Born.*—The committees gave considerable attention to problems related to the care of prematurely born infants. It was recommended that the birth weight of the infant be reported on all birth certificates and that health departments investigate the cause of each premature birth upon receipt of the birth certificate. It was pointed out that infants weighing 5½ pounds or less require special premature care. It was urged that several leading medical organizations including the American Academy of Pediatrics endorse the Children's Bureau Publication No. 292, "Standards and Recommendations for Hospital Care of Newborn Infants (Full-term and Premature)" and to use it as a criterion in the investigation of such services in hospitals. It was also recommended that State Health Departments use this publication as a criterion for approving and listing centers for the care of premature infants and where indicated to assist hospitals in establishing or enlarging such facilities.

The Committees recommended that State health departments be encouraged to purchase hospital care, transportation, pediatric, and after-care services for premature infants and for sick, newborn infants in approved centers for infants eligible for such care. Considerable emphasis was given to the importance of developing adequate professional training opportunities for physicians and nurses in the care and management of the newborn infant (premature and term) and it was urged that State health departments assist in financing such an educational program as well as providing pediatric consultation services to physicians and hospitals, in the care of the newborn infant.

*Preschool and School Health Services.*—In considering this important phase of child health services, the committees called attention to the importance of basic public health services on which to build an adequate child health program. It was recommended in view of the present lack of trained personnel, the limitation of funds, and an insufficient body of knowledge concerning the administration of a complete health program for children, that there be developed demonstration projects in which all the health needs of children would be met. As visualized by the conference members such demonstration projects would provide (1) field training of personnel for an expanding program (2) yardsticks for evaluating the effectiveness of the various components of a child health program as well as (3) rendering care of a high quality to the children in the project area. It was stated that those services directed toward the promotion of optimal physical and emotional health would constitute the basis of the program but that in addition the child would have access to complete diagnostic and consultation service and necessary treatment including hospitalization. The committees then listed a series of principles which should be observed in the development of such complete health service projects.

Attention was called to the need for developing model school health legislation in order to overcome the legal barriers which now tend to obstruct future programs in this field.

*Mental Health Services for Children.*—The committees considered the problems presented by the current dearth of trained personnel (psychiatrists, psychologists, and psychiatric social workers) in the face of increasing demands for such personnel. It was felt among the steps

which might be considered at this time in the development of mental health services for children that new child guidance clinics be developed in communities ready for such services, that present training resources be expanded and strengthened and as rapidly as training personnel becomes available new resources for training be developed; that priority for training fellowships be granted to those professional individuals who are potential teachers in this special field; that the training courses for all professional groups engaged in services for children be strengthened and broadened to insure a better understanding of the mental development of children. In this connection the committees also recommended that the Children's Bureau collaborate with the United States Office of Education regarding the inclusion of mental health services in the school health program, and that the Children's Bureau augment its professional staff in the mental health field in order to serve in an advisory and consultative capacity in the development and coordination of mental health services for children.

*Eligibility of Mothers and Children for Services Under State Programs.*—The committees discussed at some length the controversial issues involved pertaining to eligibility requirements for mothers and children seeking services under the State programs. After a thorough discussion the committees unanimously adopted among others the following statement and recommendation: "The widest diversity now exists in different States with regard to basic policies governing eligibility for services under State plans for maternal and child health and crippled children. This diversity is of an extent which can hardly be justified by existing differences of local conditions in those States. The application of basic principles should be made sufficiently flexible to meet real local limitations and opportunities so long as the fundamental human needs are met.

"One of the most fundamental human rights is the right of every individual to the maximum degree of physical and emotional health which it is possible for that individual to attain with the aid of the best scientific knowledge and technical service which are at the disposal of the Nation.

"Those knowledges and services which deal primarily with the prevention of disease, the promotion of health in the positive sense and the detection of incipient disease form a part of the basic community health program. They should be available for every person and every economic level. In regard to services of this kind, we recommend that the Children's Bureau insist that no means test be permitted in the maternal and child health and crippled children's programs.

"The treatment of disease was considered a problem of a somewhat different nature, although still a problem much more closely related to public health than to poor relief. However, wherever the funds for service of this kind are inadequate for universal coverage, it seems clear that preference should be given to those most in need. In this type of service, your Committee suggests that the Children's Bureau may properly recognize a suitably formulated criteria of economic ability if desired by individual State authorities.

"It is urged that the Bureau encourage the study and eventual development of a pattern whereby the essential medical services may be made available to all, irrespective of residence, race or economic status."

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The letter which follows was sent by Dr. Skinner in midsummer for publication in the column. On receipt of it, I wrote to Dr. Skinner urging him to withdraw it because pediatricians were tired of the controversy it revived and the letter would be productive only of ill feeling. I further pointed out, as editor of the column, the impropriety of the attacks on persons and the use of conjecture for fact. Nevertheless, in order to be absolutely fair in the conduct of the column, I informed Dr. Skinner that I would publish his letter if he insisted that I do so, and he has now written his insistence. Accordingly, I publish Dr. Skinner's letter, but with the understanding that I shall not publish replies which it might awaken.

E. A. P.

Dear Dr. Park:

In the April issue of the JOURNAL OF PEDIATRICS, I noticed the comments of Dr. Martin relative to the brochure, "Stepping Stones to Regimentation," a copy of which I am enclosing. Although I realize there can be endless controversy, it seems no more than fair to me that the medical profession should be made acquainted with the background of this pamphlet.

The EMIC Program was initiated in the State of Washington under the auspicies of the State Medical Association. Within a year it was taken completely out of our hands and, what seemed very evident to us, was used as a political extension through the emotional appeal of maternal care. Every iota of successful operation has been realized by hard working physicians who, in a majority of instances carried on under vehement protestations disdained by the Children's Bureau.

Before publishing this pamphlet for use of the state, we submitted it in the form of a questionnaire to every practicing physician in the State of Washington with the remarkable return of 32 per cent replies, some of which were quite outstanding in their stinging remarks against bureaucracy. The proposition was twofold, to inform the medical profession of what was clearly evident; the detouring of the use of a patriotic service to further political expansion, and the second, to offer a remedy. It has been the policy of our committee never to criticize without offering some logical remedy. It might be appropriate to state here that this is not the "horse and buggy era" but rather, the jet plane epoch, and it is to be recognized that this period would be of such rapidity that it would too quickly pass through the arc of some persons' intelligence and too soon be outside their ability to comprehend its passing.

It is true the bureau stated again and again that the EMIC Program would end six months after the war terminated, whenever that may be, and also that it was for an emergency only. It is reported that before a session of the executive committee of the Academy of Pediatrics this year Dr. Martha Eliot was pointedly asked if she intended to abide by her promise made again and again "to terminate the EMIC Program six months after the termination of the war." She replied "No!"

This bill is divided into three parts. I am sure that the propositions of the first two parts would meet the approval of every physician except for the fact that it definitely is to be placed without restriction, under bureaucratic administration. The third section concerns not the health, but the direction by force, if the Children's Bureau considers it necessary, to regulate every child socially in the United States from birth to the age of 21 years. It has been pointed out by a probate judge in the State of Michigan, that this is exactly the same method Hitler inaugurated in Germany, and we will be obligated to cope for years to come with the resultant Psychopathy.

That portion of the pamphlet relating to the "appointed advisory committee" *is true.* At least four members of those committees, two at one time just having come from Washington, D. C., made the statements as printed and we have no reason to question their veracity. We feel that any committee advisory to a bureaucratic setup is not well chosen except by the members of the different state medical associations throughout the United States. It is true that the Academy of Pediatrics is now conducting a very commendable survey of child health service throughout the United States. It is being intimately overseen in this state by the President of the Academy of Pediatrics and others. In addition to this, the Maternal and Child Welfare Committee with the help of the State Health Department, has been conducting an obstetrical survey throughout the State of Washington for at least four years before the war, with the result that we have some excellent records of obstetrical needs which could not be bettered by bureaucratic control and interference.

Whenever a child is sick, whether he be fifty miles from a railroad in Montana or thirty miles from a town in Texas, or in the slums of New York or Chicago, for care, either the doctor goes to him or he must come to his physician. Is there anything that a bureaucracy could stimulate to make this situation better? It is silly to contemplate a bureau in Washington releasing a directive to order the local doctor to visit the child. If the young doctor has been

cared for by the government since birth, and at the age of 21 he has been completely Russianized by the Children's Bureau Educational Scheme he will be perfectly socially minded. Yet will he have Christian compunctions with a respect for the principles of Hippocrates!

Enclosed is another pamphlet about two hundred thousand of which have been distributed mainly through the efforts of the State Medical Women's Auxiliary. Its object, as stated, is to inform the people that the bureau has very definite political designs against the people of the United States, and to offer a remedy. Apparently there are many people in the United States who believe government of the people, by the bureaus, and for the politicians is the best policy.

The so-called health bill, S.1606, was not written by physicians in the interest of United States medical care, but by Arthur Altmeyer and Isadore Falk whose concepts for United States dictatorship are well known. Bill S.1318 smacks so much of the statements and writings of Dr. Martha Eliot, and also directives issued by the Children's Bureau, that we are of the opinion that Senator Pepper never saw the bill until handed by the Bureau. These bills are for political power under the guise of "health service" empowered by the emotional appeal of maternity and child care to age 21! Any obstetrician in our opinion, or pediatrician who favors these bills is out and out for a dictatorship of the United States. This applies both to the physician who is eking out his declining years of service and intelligence in the ample armchair of complacency with sinecure emeritus of an institution, and, the poor struggling pediatrician who is misguided by the above authorities.

H. H. SKINNER, M.D.,
Chairman, Maternal and Child Welfare Committee

# Academy News and Notes

The following Fellows of the Academy have been or are about to be released from service:

*Army*

David H. Clement, New Haven, Conn.
Harry O. Davidson, Detroit, Mich.
Albert A. Frank, Malden, Mass.
Jerome S. Harris, Durham, N. C.
Oscar B. Markey, Cleveland, Ohio
Carl L. Ruder, Mt. Lebanon, Pittsburgh, Pa.
Roland Stahr, Reno, Nev.
Ralph H. Verploeg, Denver, Colo.

*Navy*

Fred W. Bush, Rochester, N. Y.
Marion G. Josephi, San Francisco, Calif.
Willard B. Rew, Yakima, Wash.
Proctor C. Waldo, Oak Park, Ill.

*United States Public Health Service and*
*United Nations Relief and Rehabilitation Administration*

Stanton Garfield, Concord, Mass.

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Captain Ernest S. V. Laub, Medical Corps, United States Navy, was transferred July 30, 1946, from the Reserve to the Medical Corps of the Navy.

# News and Notes

The following physicians have been certified by the American Board of Pediatrics following examination by the board in Cleveland, Ohio, and San Francisco, Calif.:

Herman Anfanger, Sixty-Eight Medical Regiment, Camp Forest, Tenn.
Talcott Bates, Box 107 1, Monterey, Calif.
Joseph Harold Batzle, Jr., Suite 4, 4205 Market Street, Riverside, Calif.
Richard Winston Blumberg, Station Hospital, Fort Oglethorpe, Ga.
Moses R. Buchman, 187 Fox Meadow Road, Scarsdale, N. Y.
Louise S. Childs, The Clinic, Young Street, Honolulu, Hawaii.
Homer Tullock Clay, 828 Medical Arts Building, Tacoma, Wash.
Martha Louise Clifford, 165 Capitol Avenue, Hartford, Conn.
Peter Cohen, University of California Hospital, San Francisco 22, Calif.
David Richard Davis, 103 Gazette Building, Emporia, Kan.
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George Winford McCormick, 15 Court Street, Staten Island, N. Y.
Ralph E. Moloshok, 73 East Ninetieth Street, New York, N. Y.
Marion Shaffner Morse, 134 Washington Avenue, Endicott, N. Y.
Alexander Sandor Nadas, 31 Federal Street, Greenfield, Mass.
Henry Bernard Okner, 155 South Pulaski Road, Chicago, Ill.
William W. Ornduff, 2580 Bancroft Avenue, Berkeley, Calif.
Edward L. Pratt, 300 Longwood Avenue, Boston 15, Mass.
Lawrence E. Reck, 3201 Fourth Avenue, San Diego 3, Calif.
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Herschel Sachs, 3669 Alter Place, Cincinnati 29, Ohio.
Edwin Paul Scott, 220 Monohan Drive, Louisville 7, Ky.
Amelia Burns Sheftall (Geeslin), 1022 Park Street, Jacksonville, Fla.

Bernard Harold Shulman, 1162 Union Street, Brooklyn, N. Y.
Harold I. Shuman, 483 Beacon, Boston, Mass.
William Benjamin Smith, 1125 Bradbury, Indianapolis, Ind.
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Stuart Shelton Stevenson, 1275 Post Road, Fairfield, Conn.
Robert Austin Tidwell, 205 Stimson Building, Seattle, Wash.
Stewart C. Wagoner, 1339 Union Street, Schenectady, N. Y.
Dwain Newton Walcher, 789 Howard Avenue, New Haven, Conn.
Edwin Robeson Watson, United States Marine Hospital, Mobile, Ala.
B. H. Williams, Joplin, Mo.
Edwin Thurston Williams, 1850 Gilpin Street, Denver, Colo.

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Dr. Kenneth S. Landauer has been appointed director of the division of medical care of the National Foundation of Infantile Paralysis. He will coordinate the organization's year-round program of medical care and treatment of poliomyelitis patients under supervision of Dr. Hart E. Van Riper, medical director.

Dr. Landauer has recently been director of the New York State Reconstruction Home at West Haverstraw and previous to that was director of the Cardiac Bureau of the New York State Health Department. He is a fellow of the American Academy of Pediatrics.

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Senior Fellowships for training in the field of pediatrics, administered by the Medical Fellowship Board of the National Research Council acting for the National Foundation for Infantile Paralysis, Inc., are open to physicians under 40 years of age who are citizens of the United States and who have demonstrated aptitude and promise in teaching and investigation.

These fellowships provide an opportunity, under favorable conditions, for a prolonged period of advanced training in the field of pediatrics. This training may include study and investigation in the basic medical sciences as well as clinical experience. The program throughout the period of appointment will be subject to the approval of the Medical Fellowship Board.

Original appointments are for a term of three years, but fellowships may be renewed at the discretion of the Board for an additional period not to exceed three years. During the term of the fellowship, the holder is not expected to engage in other remunerative work.

The amount of the fellowship is determined by individual circumstances and may vary from $3,000 to $6,000 a year. A sum not to exceed $1,000 annually for laboratory expenses may accompany each fellowship.

Applications for Senior Fellowships should be filed before January 1. Decision concerning awards will be made as soon as practicable after March 1.

Further particulars concerning these fellowships may be obtained on request from the Secretary of the Medical Fellowship Board, National Research Council, 2101 Constitution Avenue, Washington 25, D. C.

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The following appointments have been made in recent months, indicating changes in teaching positions in various medical schools of the country:

Dr. Franklin P. Gengenbach of Denver, Colo., has been made emeritus professor of pediatrics in the University of Colorado School of Medicine. He is succeeded by Dr. Harry H. Gordon of New York, N. Y., formerly of the Department of Pediatrics of Cornell University. Dr. Gengenbach has been president of the American Academy of Pediatrics.

Dr. Edwards A. Park has been made emeritus professor of pediatrics at Johns Hopkins University. He is succeeded by Dr. Francis F. Schwentker as professor of pediatrics. Dr. Schwentker has been in the Department of Pediatrics at the Johns Hopkins University.

Dr. Henry F. Helmholz has retired as professor of pediatrics at the Mayo Foundation and head of the section on pediatrics of Mayo Clinic at Rochester, Minn. He is a former

president of the American Academy of Pediatrics. Dr. Helmholz is succeeded by Dr. Roger L. J. Kennedy. Dr. Kennedy has been a member of the staff at Mayo Clinic.

Dr. Richard M. Smith has retired as professor of pediatrics at Harvard University Medical School. Dr. Smith has been president of the American Academy of Pediatrics. He is succeeded by Dr. Charles A. Janeway. Dr. Janeway has been a member of the staff of Harvard University Medical School.

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Fellowships leading to a Master's Degree in Public Health in the field of Health Education are being offered to any qualified United States citizen between the ages of 22 and 40, according to a statement released Nov. 12, 1946, by the United States Public Health Service, Federal Security Agency. Tuition, travel expenses for field training, and a stipend of $100 a month will be provided out of funds furnished by the National Foundation for Infantile Paralysis.

Candidates must hold a Bachelor's Degree from a recognized college or university and must be able to meet the entrance requirements of the accredited school of public health of their choice. In addition to the degree, courses in the biological sciences, sociology, and education may be required. Training in public speaking, journalism, psychology, and work in public health or a related field are considered desirable qualifications.

The year's training, which begins with the 1947 fall term, consists of eight or nine months of academic work including: public health administration, epidemiology, public health and school education, problems in health education, community organization, and information techniques; and three months of supervised field experience in community health education activities.

Application blanks may be obtained by writing to the Surgeon General, United States Public Health Service, Washington 25, D. C., and must be filed prior to March 15, 1947.

Veterans are encouraged to apply and will be paid the difference between their subsistence allowance under the G. I. Bill of Rights and the monthly stipend of $100. Employees of local and state health departments are not eligible since Federal grants-in-aid are already available for such training purposes.

# Book Reviews

**Courage and Devotion Beyond the Call of Duty.** Second preliminary Edition, Evansville, Ind., 1946, Mead-Johnson & Co.

The second "preliminary" edition of the record of official citations to medical officers in World War II now contains over 900 individual citations and about fifty group citations. There are still a great number missing, as a local check disclosed. When the book is completed it will be a most valuable and interesting record of the splendid work of the doctors in the armed forces in the late war.

**The Health of the School Child.** Gertrude E. Cromwell, R.N.M.S., Philadelphia, 1946, W. B. Saunders Company, 256 pages. Price $2.50.

This book contains a little about a great many things. While the purpose is to give a clearer understanding to the nurse, it contains material having to do with school architecture etc., which hardly comes within the function of the nurse. Some sections have been so condensed in order to cover a tremendous field in a brief text that the material is decidedly sketchy. The author has had a vast personal experience and training in school nursing and its relationship to other school activities. It would seem to the reviewer that it would be an excellent text to feed to the lay members of our school boards who, as a whole, are politically minded rather than school minded and have little conception of a school health program.

# Comment

## THE ACADEMY STUDY OF CHILD HEALTH SERVICES

When the Academy's Committee for the Study of Child Health Services was given the official green light signal at the St. Louis session in November, 1944, the general opinion, as expressed at its first organizational meeting, was that a budget of some $20,000 to $25,000 would probably be sufficient to finance a survey of existing child health facilities and services in the United States, and would point up those deficiencies most urgently needing attention upon which a cooperative action program between governmental agencies (particularly the Children's Bureau) and the Academy could be based.

Last month, on October 1, this same committee met in Washington, D. C., to review the progress of the survey and to make plans for the future. It learned that the originally estimated, rather microscopic budget had, in the two-year interval, grown to the adult proportions of around $1,000,000. How did this tremendous increase in magnitude over the original estimations come about? There are many factors involved, but the main answer is to be found in the kind of job that is being done. This is the first time that a medical organization has ever undertaken a project of this kind. The usual sampling method has not been employed by John Hubbard and his able staff. Actual details have been collected for every city, town, hamlet, and for every county in the United States, concerning hospital facilities, physicians' and dental services, and voluntary and official community health service, both from a quantitative and qualitative point of view. Even the number of telephone calls per day (and night) which the harassed dispenser of child health services must sandwich in between all the other demands upon his time and good nature will be known. In addition to these fundamental questions, Dr. James Wilson is heading another phase of the study which is a thorough inquiry into the status of undergraduate and postgraduate pediatric education as it exists in our medical schools and hospitals today.

When the collection of factual data is completed, some 250,000 schedules will be in the hands of the central office in Washington for statistical analysis and tabulation. Instead of employing one person for a hundred years to do this job, Dr. Hubbard tells us that sixty girls, plus some miraculous machines that need only a few minor adjustments to raise them to human levels, will complete the task in approximately six months. Obviously, when the statistical portion of the study is completed, there will be available a tremendous volume of factual data concerning facilities and services for children as well as the deficiencies in various areas. Already it can be said that this portion of the survey is an assured success.

If, at this point, we begin to wonder whether this huge investment, largely of other people's money which has been invested in the Academy's study, plus

the time and effort of a great many people, is worth the price, let us see what others think. The National Foundation for Infantile Paralysis has backed us by an outright grant of some $116,000, and many thousands of dollars more have been given by local chapters in the various states. For the first time in its history, the National Institute of Health has departed from its established custom of restricting its funds to purely scientific projects to assign a sizeable sum ($128,000) to a social study. The Field Foundation, Mead Johnson and Company, Lederle Laboratories, Inc., M & R Dietetic Laboratories, Inc., Pet Milk Company, and Carnation Company have all demonstrated their confidence in the Academy's project by making substantial contributions. Without the very generous and especially skilled aid of the U. S. Public Health Service and the Children's Bureau, the study would not have been possible. This harmonious and effective attack upon an important national health problem by a combination of governmental agencies and physicians is a real achievement pointing the way to the solution of the problem of improving the health facilities and services for all our people. And last but not least, there are the state chairmen who, together with their executive secretaries and pediatric confreres, have done and are doing a magnificent job in the actual collection of data at the local level. The combined State budget which these state chairmen have raised amounts to approximately $450,000. At Washington it was the good fortune of the members of the National Committee to observe the state chairmen in session at the third of the regional conferences. Each of us, I am sure, was impressed and stimulated by the enthusiasm and determination which was manifest on every hand. All this adds up to the inescapable conclusion that a great many important people have confidence in the project the Academy has taken on. Is it worth while? These people think so, and they have backed up their belief with their dollars and with their personal participation. That every Academy member believes so, there is not the slightest doubt. Furthermore, I am certain that all of us in the Academy fully realize the responsibility, the opportunity, and the challenge which faces us in order that those who have reposed their confidence in us are not let down. The information which has been collected in the survey must be implemented into an action program, or much of the effort which has gone into the statistical phase of the study will have been wasted. The Academy has no intention of letting such a catastrophe come to pass.

The greater portion of the Committee's deliberations in Washington was concerned, not with the survey itself, but with the utilization of the factual data which will be available some time late in 1947 or early in 1948. It was the feeling of the present Committee that its function would come to an end with the publication of the statistical material at both national and state levels. A recommendation is being made to the Executive Board of the Academy that a new representative Committee be established and charged with the responsibility of interpretation of the collected data, setting up standards for comparison purposes at any given locale, and even more fundamental, preparing the blueprints for a long-time, cooperative action program designed to achieve the mutually desired objective stated in the Academy's first report; namely, "To make available to all mothers and children of the United States all essential preventive,

diagnostic, and curative medical services of high quality, which, used in cooperation with other services for children, will make this country an ideal place for children to grow into responsible citizens."

Many of us objected to the government-sponsored bills introduced into the last session of Congress on the grounds of political domination, unworkability, likelihood of lowering standards of medical practice, probability of abolishment of private practice, and antagonism and therefore noncooperation on the part of the general medical profession in what it was felt was "socialized medicine." Furthermore, there was the additional objection that none of these proposed bills bore any relation to specifically demonstrated needs.

The survey being completed offers a new approach to the whole problem of improvement of child health. Facts, and many of them, are going to made known about deficiencies in facilities and services, facts which have been obtained by physicians themselves. In correcting these deficiencies, legislation is going to be needed, but it will be legislation with a known purpose, based on these facts. There is every reason to believe that the Academy and the governmental agencies which have cooperated so splendidly in the statistical analysis will, in the same sort of a joint effort, go forward in the next phase of the program—implementation and action.

The conclusion that ought to be reached, it seems to me, is that instead of completing a task it set out to do, the Academy has but taken the first step. True, that first step has been a big one and an important one, but there must follow many more steps equally vigorous and equally important.

LEE FORREST HILL

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